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American Heart Journal

VOL. 35 APRIL, 1948 NO. 4

Original Communications

CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE

AN ANALYSIS OF THE REASONS FOR LACK OF CLOSE CORRELATION BETWEEN THE SYMPTOMS OF HEART FAILURE AND THE RESTING CARDIAC OUTPUT

EUGENE A. STEAD, JR., M.D., DURHAM, N. C., JAMES V. WARREN, M.D., ATLANTA, GA., AND EMMETT S. BRANNON, M.D., ROME, GA.

THE function of the heart is to pump blood to the various organs and tissues of the body. When the heart action becomes inadequate, the familiar picture of congestive heart failure develops. Though there has been general agreement that the cardiac output in congestive failure is decreased,[1] it has not been possible to correlate the symptomatology of the patient with the absolute level of the cardiac output. The development of the technique of right heart catheterization has simplified the measurement of the cardiac output in acutely ill patients. The cardiac output is calculated from the Fick principle by dividing the oxygen consumption per minute by the arteriovenous oxygen difference. Arterial blood is obtained from any convenient artery by direct puncture and mixed venous blood is obtained by the catheter from the pulmonary artery, right ventricle, or right atrium. With this new tool, it seemed worthwhile to reinvestigate the relation between the cardiac output and the symptoms of congestive failure.

METHOD

The right heart was catheterized via the median antecubital vein.[2-4] The oxygen content of the mixed venous blood was determined on samples collected from the pulmonary artery, right ventricle, or right atrium. The mean atrial pressure was recorded in centimeters of saline, a point 5.0 cm. below the fourth costochondral junction being taken as reference point. Samples of arterial blood

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were obtained from the brachial or femoral artery, and the arterial pressure was recorded by the method of Hamilton and associates.[5] The oxygen content of the blood was determined by the method of Van Slyke.[6] The oxygen consumption per minute was determined by collecting the expired air for two- or three-minute periods and analyzing a sample for oxygen by the method of Haldane.[6] The cardiac output is recorded as liters per minute. The cardiac index is the cardiac output per liter per minute per square meter of body surface. Heparin was used as the anticoagulant for determining the hematocrit reading. The total protein concentration was measured by the falling drop method.

RESULTS

Normal Subjects.—The cardiac output was measured sixty-six times in sixty-one normal subjects. The determinations were done in the morning with the subject in the recumbent position and after a twelve-hour fast. Subjects who had a hemoglobin concentration below 10 Gm., or a hematocrit reading below 25, or who had evidence of heart or lung diseases were not included. Otherwise, there was no selection. The subjects were doctors and medical students working in the hospital, and patients convalescing from elective surgery or respiratory infections. The relevant data on these subjects are given in Table I. No difference was apparent in the values for cardiac output in the convalescent patients and the hospital personnel. Every effort was made to keep the subjects comfortable and to relieve apprehension. While subjects who had shown signs of anxiety previous to the time of catheterization were not selected, no subject was excluded from this series because he showed evidences of anxiety during the test, as we were interested in establishing the range of cardiac output which would be found in sixty-six consecutive determinations on normal subjects. The average arteriovenous oxygen difference was 4.1 volumes per cent and the average cardiac index was 3.6. These values are not significantly different from those previously reported for a smaller group of normal subjects who showed no evidence of anxiety. While a few subjects in the series reported here had very high cardiac indices because of their emotional reaction to the test, they were in the distinct minority and did not significantly modify the average values.

Patients With Congestive Heart Failure.—The cardiac output was measured fifty-four times in forty-eight subjects in congestive failure (Table II). The determinations were usually done in the morning after a twelve-hour fast. A few patients were studied immediately after admission to the hospital. These patients had usually been too sick to eat much food during the day of admission and there was no difference in the results in these patients. If the patient was uncomfortable in the recumbent position, the trunk was supported at a 30° angle by a back rest. Patients were not included in this series unless the hemoglobin concentration was above 10 Gm. and the hematocrit reading above 25. Patients with thyrotoxicosis or ateriovenous fistulas were excluded.

The cardiac output in the patients with heart failure was lower than in the normal subjects. There was much less overlap than was anticipated. The cardiac output was below 4.5 liters per minute in forty-two, or 78 per cent of the de-

terminations in patients with heart failure. It was above 4.5 liters in fifty-four, or 82 per cent of the determinations in normal subjects.

The age distribution of the normal and cardiac subjects was not comparable. There were many more normal subjects between the ages of 20 and 30 years and few were older than 40. In the age group between 29 and 40 years, there were twenty-one normal subjects and eighteen cardiac patients. A comparison of the values for cardiac output in these two small groups with relatively comparable ages shows the same differences between the normal subjects and the patients with congestive failure that were evident in the groups as a whole.

As the cardiac patients had varying amounts of edema and many of them never became edema-free, the true surface area could not be calculated with any exactness. The surface area was calculated from the patient's height and from his weight at the time of the observations. To eliminate the factor of edema, the cardiac outputs were plotted against height in normal and cardiac subjects. The results obtained were similar to those found by plotting against surface area.

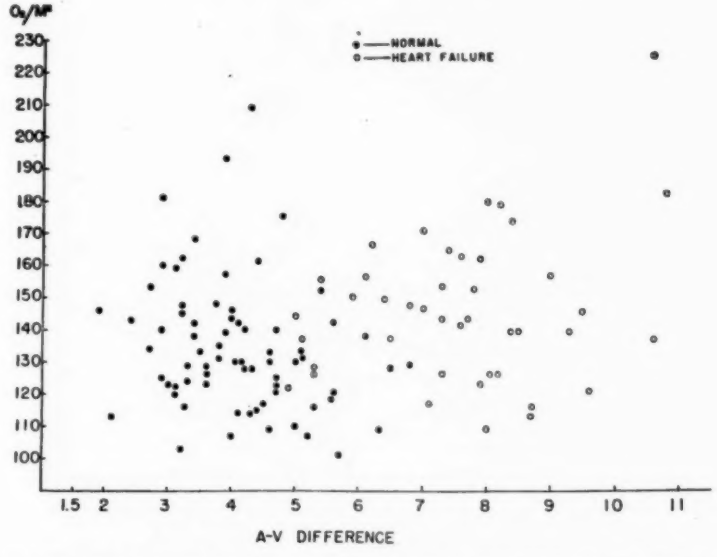

Fig. 1.—Relation between oxygen consumption and arteriovenous oxygen difference in normal subjects and patients with congestive heart failure.

The arteriovenous oxygen difference gives a rough index of the relationship between the metabolic demands of the body and the efficiency of the circulation. In the patients with congestive heart failure, the arteriovenous oxygen difference was greatly increased. Forty-eight, or 89 per cent, of the determinations in patients with failure had an arteriovenous oxygen difference greater than 5.2 volumes per cent. Only nine, or 14 per cent, of the determinations in normal subjects showed an arteriovenous oxygen difference greater than 5.2 volumes per cent. (Fig. 1).

TABLE I. DATA ON CIRCULATION IN NORMAL SUBJECTS. DETERMINATIONS WERE MADE IN MORNING AFTER TWELVE-HOUR FAST. SOME SUBJECTS WERE NOT RELAXED AS SHOWN BY HIGH OXYGEN CONSUMPTION, RAPID PULSE RATE, AND ELEVATED SYSTOLIC PRESSURE

SUBJECT	AGE (YR.)	SEX	SURFACE AREA (SQUARE METERS)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIO-VENOUS OXYGEN DIFFERENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)
C. A.	23	M	1.88	71	138	3.9	6.6	3.5
J. A.	33	M	1.94	71	168	3.4	9.6	4.9
R. A.	22	F	1.76	69	148	3.7	7.0	4.0
C. B.	23	M	1.90	73	123	3.0	7.8	4.1
W. B.	27	M	1.76	73	143	2.4	10.5	6.0
H. B.	26	M	1.99	73	147	3.2	9.1	4.6
E. C.	14	M	1.76	70	120	5.6	3.8	2.2
O. F.	41	F	1.55	63	131	5.2	3.9	2.5
M. H.	39	F	1.91	70	124	4.7	5.0	2.6
B. J.	39	M	1.86	68	128	3.6	6.5	3.5
I. L.	29	F	1.63	64	125	2.9	7.0	4.3
N. P.	37	F	1.59	64	113	2.1	8.6	5.4
S. S.	35	F	1.59	63	123	3.6	5.4	3.4
W. M. S.	44	F	1.73	66	114	4.1	4.8	2.8
J. W.	42	M	1.68	66	152	5.4	4.7	2.8
E. W.	58	F	1.60	63	133	4.6	4.6	2.9
W. A.	23	M	1.86	70	116	5.3	4.1	2.2
J. B.	30	M	2.04	71	140	4.2	6.8	3.3
J. S.	30	M	1.75	68	122	4.7	4.5	2.6
V. M.	18	M	1.77	66	145	3.2	8.0	4.5
O. F.	31	M	1.87	71	129	6.8	3.6	1.9
A. R.	40	M	1.87	73	175	4.8	6.8	3.6
T. B.	23	M	1.88	71	119	5.6	3.9	2.1
H. A.	21	M	1.77	71	157	3.9	7.1	4.0
L. H.	38	M	1.69	68	117	4.5	4.4	2.6
L. H.					107	4.0	4.5	2.7
J. A. J.	32	M	1.87	71	133	5.1	4.8	2.6
J. H.	30	M	1.58	61	209	4.3	7.7	4.9
J. A. H.	19	M	1.82	71	134	2.7	9.0	4.9
E. A.	30	M	1.81	68	142	3.4	7.7	4.2
N. A.	33	M	1.75	70	130	4.6	5.0	2.9
L. R.	22	M	1.95	72	116	3.3	6.9	3.5
J. B.	36	M	2.00	69	127	3.6	7.1	3.6
L. L.	16	M	1.73	68	142	5.6	4.4	2.5
W. W.	57	M	1.73	66	129	4.2	5.3	3.1
F. W.	23	M	1.98	72	106	5.7	3.8	1.9
M. S.	22	M	1.68	68	128	6.5	3.4	2.0
J. P.	22	M	1.80	70	110	5.0	4.0	2.2
C. G.	22	M	1.73	68	124	3.3	6.6	3.8
W. F.	24	M	1.81	69	107	5.2	3.6	2.1
*E. S.	35	M	2.04	73	109	4.6	4.9	2.4
*W. M.	23	M	1.90	71	103	3.2	6.1	3.2
*W. M.					120	3.1	7.4	3.9
*W. L. M.	22	M	2.04	73	121	4.7	5.3	2.6
*C. G.	22	M	1.91	74	131	3.8	6.5	3.4
*W. S.	25	M	2.04	73	133	3.5	7.7	3.8
*W. F.	23	M	1.85	71	114	4.3	4.9	2.7
*M. S.	22	M	1.87	70	130	5.0	4.9	2.6
*R. G.	23	M	1.98	72	129	4.2	6.1	3.1
*W. B.	23	M	1.93	71	146	1.9	14.8	7.7
*W. B.					122	3.1	7.6	3.9

TABLE I. DATA ON CIRCULATION IN NORMAL SUBJECTS. DETERMINATIONS WERE MADE IN MORNING AFTER TWELVE-HOUR FAST. SOME SUBJECTS WERE NOT RELAXED AS SHOWN BY HIGH OXYGEN CONSUMPTION, RAPID PULSE RATE, AND ELEVATED SYSTOLIC PRESSURE—CONTINUED

SUBJECT	AGE (YR.)	SEX	SURFACE AREA (SQUARE METERS)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIO-VENOUS OXYGEN DIFFERENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)
*L. M.	30	M	1.84	67	138	6.1	4.2	2.3
*B. J.	25	M	1.99	71	140	4.7	5.9	3.0
*H. B.	26	M	1.99	73	159	3.2	9.9	5.0
*J. C.	16	M	1.69	70	130	4.1	5.4	3.2
*P. M.	17	M	1.78	67	143	4.0	6.4	3.6
*C. L.	33	M	1.77	69	135	3.8	6.3	3.6
*S. L.	27	M	1.76	67	129	3.3	6.8	3.9
*G. H.	39	M	1.93	70	130	4.1	6.3	3.3
*J. F.	27	M	1.63	65	146	4.0	6.0	3.7
*Y. W.	25	M	1.82	70	138	3.4	7.4	4.1
*W. P.	32	M	1.74	65	162	3.2	8.8	5.1
*W. P.					153	2.7	9.9	5.7
*W. P.					142	4.1	6.0	3.4
*J. T.	31	M	1.84	69	181	2.9	11.5	6.2
*I. R.	22	M	1.84	68	160	2.9	10.2	5.5

*Data reported in J. Clin. Investigation 24:326, 1945.

The degree of dyspnea and orthopnea and the atrial pressure reading varied greatly in this series, depending upon whether salt had been restricted in the diet and a mercurial diuretic administered. These patients were either in chronic heart failure, requiring salt restriction and the biweekly administration of a mercurial diuretic to remain comfortable, or they were new admissions to the hospital who were studied before therapy. In general, the group was composed of patients with severe heart failure.

The atrial pressure, arterial pressure, and pulse rate could not be correlated with the symptoms or with the cardiac output. The etiology of the heart disease made no difference in the findings. Equally severe reductions in cardiac output were found in all of the common types of heart disease (Table I).

Response to Lanatoside C.—Patients with congestive failure who had not been receiving digitalis were given 1.6 mg. of lanatoside C intravenously. This produced a decrease in arteriovenous oxygen difference, an increase in cardiac output, and a rapid fall in atrial pressure which was not dependent on a change in blood volume. The amount of subjective relief which occurred in the first hour after the drug was given was quite variable. Regardless of the rise in cardiac output, the patients always remained dyspneic and orthopneic, though in some these symptoms were less marked. These observations will be reported in detail elsewhere. At present, it is sufficient to emphasize that symptoms of dyspnea and orthopnea persisted after the cardiac output was increased by lanatoside C. The

TABLE II. STUDIES OF THE CIRCULATION IN PATIENTS WITH CONGESTIVE HEART FAILURE

SUBJECT	AGE (YRS.)	SEX	SURFACE AREA (SQUARE METERS)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIAL OXYGEN SATURATION (PER CENT)	ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT)	MIXED VENOUS OXYGEN CONTENT (VOLUMES PER CENT)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOLUMES PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)	ATRIAL PRESSURE (MM. H_2O)	ARTERIAL PRESSURE (MM. HG)			HEART RATE (BEATS PER MIN.)	HEMOGLOBIN (GM. PER 100 C.C.)	HEMATOCRIT READING (PER CENT)	TOTAL PROTEIN (GM. PER 100 C.C.)	DIAGNOSIS
													SYSTOLIC	DIASTOLIC	MEAN					
M. R.																				
11- 8-43	45	M	1.58	65	141		18.9	11.3	7.6	2.9	1.8	15	164	60	93	94	14.1			SAI
2-24-44			1.66		139		14.5	6.0	8.5	2.7	1.6		190	70	105	96	12.1		5.3	
K. Mc.	49	F	1.94	68	155		18.8	13.4	5.4	5.6	2.9	112	200	100		75	15.9	52.0	6.1	HHD
V. L.	14	F	1.34	62	164	94	13.7	6.3	7.4	3.0	2.2	200	105	58	70	100	11.4	39.0	5.3	RHD
M. B.																				
12- 3-43	33	M	2.08	75	122	91	18.9	14.0	4.9	5.2	2.4	25	184	124	145	88	14.5	54.0		HHD
12-31-43			2.19		150	93	13.7	7.9	5.8	5.7	2.6	295	203	122	148	79	11.0			
4-15-44			2.28		126		16.3	8.2	8.1	3.5	1.5	300	197	128	150	79	13.2	47.0		
L. L.	51	F	1.63	64	147		13.4	6.6	6.8	3.5	2.1	110	202	118	139	79	11.7	40.0		HHD
J. D. P.	32	M	2.04	78	137		16.3	9.8	6.5	4.3	2.1	70	140	98	110	107	13.5	45.0	7.0	HHD
E. L.	68	F	1.53	63	139	80	15.6	6.3	9.3	2.3	1.5	140	162	88	109	100	13.9	53.5		HHD
L. H.	41	M	1.91	71	149	79	13.7	7.3	6.4	4.4	2.3	195	116	72	80	104	12.3	41.8	3.8	RHD—MS
J. R.	63	F	1.47	62	137		16.1	5.5	10.6	1.9	1.3		192	94		88				HHD and AHD
F. M.	51	M	1.96	66	173	81	13.9	5.5	8.4	4.0	2.0	250	208	133	155	86	12.7	41.2		HHD
E. M.	56	M	1.56	64	156		16.5	10.4	6.1	4.0	2.6	30	124	60		94	12.2	31.3		RHD—MS
A. H.	62	F	1.55	64	126		13.5	8.2	5.3	3.7	2.4	95	174	64	100	88	11.3	36.0	5.3	SAI
C. P.	43	F	1.80	64	113	94	14.7	6.0	8.7	2.3	1.3	185	102	82	83	178	11.9	38.0		Parox. aur. tachy.
A. W.	58	M	2.10	70	145	90	17.2	7.7	9.5	3.2	1.5	220	137	100	108	112	13.5	47.0	5.0	AHD
J. H.	42	M	1.92	71	182		16.6	5.8	10.8	3.2	1.7	150	202	73	112	84	13.9	44.0		SAI
N. J.	39	F	2.21		179		12.5	4.5	8.0	4.9	2.2	300	195	87	126	112	11.5	26.0	6.7	RHD—MS
W. F.	48	M	1.82	71	143		16.0	8.3	7.7	3.4	1.9	245	168	78	114	88	10.9			SAI
A. J.	37	M	2.12	67	178		18.8	10.6	8.2	4.6	2.2	150	175	107	133	88	15.6	51.0		HHD
E. M.	33	M	1.96	67	153		15.1	7.8	7.3	4.1	2.1	270	158	97	119	111	12.5	46.4		HHD
W. A.	26	M	2.04	61	152		16.1	8.3	7.8	4.0	2.0	50	175	120	137	84	13.2	42.0		HHD
C. Mc.	63	M	1.82	66	166		15.2	9.0	6.2	4.9	2.7	135	200	130	152	94	12.8	41.8		HHD
H. M.	34	M	1.96	71	146		16.2	9.2	7.0	4.1	2.1	125	142	48	87	120	12.7	44.0		SAI
S. H.	45	F	1.94	68	144		14.3	9.3	5.0	5.6	2.9	140	131	75	89	104	11.9	41.0	6.2	RHD—MS

J. C.	54	M	1.58	65	161		15.2	7.3	7.9	3.2	2.0	60	200	44	89	79	11.4	37.0	5.7	SAI
W. L.	47	M	1.65	64	137		15.1	9.9	5.2	4.3	2.6	35	112	46	72	84	13.1	38.0	5.5	SAI
S. J.	33	M	1.77	65	170	71	10.6	3.6	7.0	4.3	2.4	160	115	75	87	100	11.8	38.0	5.3	Unknown
H. H.	46	M	2.00	72	225		16.7	6.1	10.6	4.2	2.1	160	265	86	151	100		48.0		SAI
F. P.	33	M	1.77	65	128		13.5	8.2	5.3	4.3	2.4	50	185	102	123	88	11.1	41.0	5.4	AHD
J. J.	30	M	1.75	67	121	92	15.0	5.4	9.6	2.2	1.3	215	137	97	105	124	12.1	42.8		RHD—MS
L. P.	39	M	1.96	73	117		20.2	13.1	7.1	3.2	1.6					52	15.5	50.0	5.9	RHD—MS
A. P.	40	M	1.90	72	109	85	14.4	6.4	8.0	2.6	1.4	290	89	66	69	104	11.8	42.0	4.2	AHD
R. W.	49	M	1.90	68	126		14.9	7.6	7.3	3.3	1.7	120	147	102	114	104	12.1	39.C	5.4	AHD
M. W.	56	F	1.75		139		14.8	6.4	8.4	2.9	1.7	130	139	87	100	88	12.8	40.3	4.9	RHD—MS
J. M. L.																				
12- 7-43	34	F	1.56	61	156		16.4	7.4	9.0	2.8	1.8	210	188	36			13.6			RHD—MS
7-11-45			1.64		126		15.2	7.1	8.1	2.6	1.6	210	183	43	85	64	12.6	40.0		RHD—MS
W. S.	40	M	1.69	66	162		14.1	6.5	7.6	3.1	1.8	245	212	51	97	94		40.0	5.7	SAI
J. M.	54	M	2.42	69	143		22.8	15.5	7.3	4.7	1.9	205	183	101	127	94	18.1	47.8	4.9	HHD
A. M. W.	36	F	1.91	68	116		14.6	5.9	8.7	2.5	1.3		178	66	99		10.6	39.5		SAI
T. S.	54	M	1.85		123		14.4	6.5	7.9	2.9	1.6	215	108	80	86	120	11.5	38.0	3.7	RHD—MS
H. S.	37	M	1.70	66	125	94	17.9	11.7	6.2	3.4	2.0		150	80		55		40.8	6.1	SAI
J. G.	63	M	1.61	66	160	91	17.5	11.1	6.4	4.0	2.5	6	148	94		86		46.8	6.5	HHD
L. V. E.	41	M	1.61	66	201	96	14.2	8.3	5.9	5.5	3.4		150	60		76		35.2	6.3	SAI
I. D.	64	F	1.86	66	184		16.4	8.6	7.8	4.4	2.4	22	170	100		140		42.0	5.3	HHD
L. B.	52	M	1.55	65	163	93	17.1	10.5	6.6	3.8	2.5	6	220	80		52		43.8	5.8	HHD and RHD—MS
J. C.	32	M	2.00	73	141		12.9	5.4	7.5	3.8	1.9	70	135	60	78	88	10.1	36.6	4.3	SAI
G. H.	57	M	1.64	69	129		14.1	10.9	3.2	6.6	4.0	0	148	44	70	91	12.3	43.0	4.0	SAI
T. T.																				
2-27-44	37	F	1.45	64	128		16.9	9.1	7.8	2.3	1.6	185	206	117	143	88	12.0	38.0	6.5	HHD
12-23-44			1.56		154		15.5	5.2	10.3	2.3	1.9	295	206	141	163	94	11.2	39.2	6.8	
10- 9-46	40		1.64		144		16.5	12.2	4.3	5.9	3.6		160			78				
L. F.	35	F	1.44	64	131		14.5	7.5	7.0	2.7	1.9	170	156	34	64	71		38.5		SAI
G. D.	55	M	1.88	66	125	76	11.7	6.5	5.2	4.5	2.4	18	197	54	92	68	11.5	37.1	6.2	SAI

SAI—Syphilitic aortic insufficiency.
HHD—Hypertensive heart disease.
RHD—Rheumatic heart disease.
MS—Mitral stenosis.
AHD—Arteriosclerotic heart disease.

disappearance of the dyspnea was dependent on the relief of pulmonary edema. It takes some time for the wet lungs to become dry even though the cardiac output in certain instances may be brought quickly to an adequate level by digitalis.

Patients With Congestive Heart Failure and Severe Anemia or Thyrotoxicosis.—Observations were made on two patients with severe anemia and heart failure. One was anemic because of severe menorrhagia, and the second because of renal failure. The atrial pressure was greatly increased and dyspnea, orthopnea, and edema were marked. The cardiac outputs were considerably higher than would have been expected in a normal subject of the same size and height (Table III). Similar observations were recorded in two patients with thyrotoxicosis and heart failure Table (III). Both severe anemia and thyrotoxicosis cause a great increase in the cardiac output under basal conditions. It is to be expected, therefore, that congestive failure might develop long before the resting output fell to the level found in normal subjects.

DISCUSSION

The occurrence of high atrial pressure and congestive failure in the presence of an elevated cardiac output in the patient with anemia or thyrotoxicosis is of considerable interest. We have pointed out before that the damming back of blood behind the right ventricle because of heart failure is not an adequate explanation for the rise in venous pressure.[7] Since the blood circulates in a closed system, the left ventricle can pump to the right ventricle only the blood which has been pumped to it by the right ventricle plus that amount of blood which can be delivered to the left ventricle, independent of the right ventricle, by active vasoconstriction in the lungs. There is no evidence that vasoconstriction in the lungs can push any large amount of blood into the systemic circulation. The rise in venous pressure in these patients appears to be related to the increased blood volume which occurs in chronic congestive failure and to venoconstriction which occurs in the presence of an inadequate output of the left ventricle. The possible explanations for such venoconstriction have been recently summarized by Merrill and associates.[8]

The cardiac output of normal subjects is increased above the normal resting level by work and by apprehension.[4,11] Which of these factors is at work to increase the cardiac output can frequently be determined by observing the oxygen consumption and arteriovenous oxygen difference.[11] Work results in a sharp increase in oxygen consumption and a slight widening of the arteriovenous oxygen difference. Apprehension results in a considerable decrease in arteriovenous oxygen difference and a smaller rise in oxygen consumption. When the oxygen consumption per square meter is plotted against the arteriovenous oxygen difference (Table I), it is apparent that increased oxygen consumption in the normal subjects is associated with a marked decrease in arteriovenous oxygen difference, indicating that these subjects were apprehensive. In the patients with cardiac failure, high levels of oxygen consumption were associated with large arteriovenous differences (Table II), indicating that the circulation was inadequate for the

TABLE III. HIGH CARDIAC OUTPUT IN CONGESTIVE FAILURE WITH SEVERE ANEMIA AND THYROTOXICOSIS

SUBJECT	AGE (YR.)	SURFACE AREA (SQUARE METERS)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)	VENOUS OXYGEN CONTENT (VOLS. PER CENT)	ARTERIO-VENOUS OXYGEN DIFFERENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)	ATRIAL PRESSURE (MM. OF H_2O)	HEMATOCRIT READING	DIAGNOSIS
B. S.	46	1.8	143	2.8	1.3	1.5	17.0	9.4	200	9	Anemia from menorrhagia
A. M.	39	1.38	138	6.3	3.2	3.1	6.1	4.5	225	16	Hypertension and uremia
P. W.	55	1.44	202	12.8	9.4	3.4	8.6	6.0	155	42.4	Thyrotoxicosis
N. H.	39	1.53	255	10.1	7.1	3.0	8.5	5.6	250	33	Thyrotoxicosis

metabolic needs of the body at the time of the study. The abnormally large arteriovenous oxygen difference at rest is probably a better indication of the actual inadequacy of the circulation than is the absolute level of the cardiac output.

The finding of a reduced cardiac output in patients with uncomplicated congestive heart failure agree with the results of other investigators using the Fick principle. McGuire and collaborators[9] obtained blood from the heart of several patients by direct puncture. The South American investigators[2] obtained blood from the right atrium by cardiac catheterization. Harrison[1] and Stewart and Cohn,[10] using the acetylene method, found a reduced cardiac output and an increased arteriovenous oxygen difference in patients with moderately severe congestive failure.

It is rather surprising to find such uniform agreement among the various investigators who have measured the cardiac output in congestive failure. The conditions under which the data are collected are such as to minimize the differences between a normal and a failing circulation. The cardiac subject at rest in the basal state may have an entirely normal output and still have easily demonstrable circulatory failure on mild exertion.[12] The reserve in the cardiovascular system is in the direction of increasing the cardiac output. The output does not have to be reduced far below the resting level to produce signs of circulatory failure in the normal subject.

While there is general agreement that the cardiac output in congestive failure is reduced, there has been less agreement as to the relation between the reduction of cardiac output and the symptoms of heart failure. Most investigators have found no constant relationship between the absolute level of the cardiac output and the presence of dyspnea, orthopnea, and edema. Our findings are similar.

This lack of correlation between the absolute level of the cardiac output and the symptoms of failure is shown most strikingly in the data collected on the patients with heart failure complicated by anemia and thyrotoxicosis. The patient with severe anemia and heart failure will have a high cardiac output at rest in the presence of all the usual signs and symptoms of severe congestive heart failure. If his anemia is controlled, the cardiac output will decrease and the signs of failure will disappear. This same sequence of a high cardiac output with failure and a low cardiac output with compensation is seen in heart failure produced by thyrotoxicosis. The thyrotoxic patient with failure has a high output at rest, but because it is not high enough to satisfy the needs of his increased metabolism, failure occurs. If the hyperthyroidism is satisfactorily treated, the requirements of the body for blood are greatly decreased. The cardiac output falls to a normal level, but the output is now adequate for the body needs and compensation occurs.

At first, the concept that certain patients develop congestive failure with a high cardiac output and compensate with a smaller cardiac output appears strange. A little reflection leads us to the conclusion that this is a common occurrence. The cardiac output during the usual daily working routine is considerably

elevated over the basal level. Most patients develop failure during activity. At that time the cardiac output is above the resting level but is inadequate for the needs of the active patient. On resting the cardiac output falls as in a normal subject. With the reduction of the need for blood the output is now adequate, and the subject compensates with an output considerably lower than that present while he was decompensating.

The restless, dyspneic, ill patient with failure may have an abnormally large requirement for blood as demonstrated by a high arteriovenous oxygen difference in the presence of an output equal to that of a normal resting subject. If the water logging of the lungs is relieved by sodium restriction and if the patient becomes quiet and is able to breathe normally, the patient may remain compensated at rest with the same cardiac output as on admission. That compensation at rest has occurred may now be demonstrated by the fact that the patient can eat large amounts of salt without forming excessive edema. If the apprehension and restlessness on admission were particularly severe, he may remain compensated at rest with an even lower output than he had on admission.

The symptoms due to retention of fluid in the lungs may persist after the output has become adequate. For example, a patient treated with digitalis may quickly increase his cardiac output to a level adequate to cause a rapid diuresis. Nevertheless, many of the symptoms of waterlogged lungs will remain until the kidneys have removed the retained salt and water.

If the cardiac output is measured at rest the following combinations may be expected to exist:

1. Cardiac output low with failure; remains low with the disappearance of symptoms. Symptoms will be relieved by sodium restriction and continued use of diuretics. Majority of patients reported in this paper fall into this classification.
2. Cardiac output low with failure, increases with administration of digitalis or when such complications as pulmonary infarctions clear up. Does not require salt restriction or diuretics when activity is reduced by bed rest.
3. Cardiac output normal with failure; remains normal on compensation. Decompensation develops with increased activity. Cardiac output adequate at rest; symptoms at time of study present because of waterlogging of the lungs, which will persist until diuresis is completed.
4. Cardiac output high with failure; falls with compensation. This combination is present in (a) restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for apprehension and mild exertion and (b) patients with hyperthyroidism, anemia, arteriovenous fistulas, patent ductus arteriosus, beriberi, and certain infections.

Thus, it appears that symptoms of congestive failure develop whenever the cardiac output is inadequate for the demands of the tissues over a prolonged period of time and that there is no absolute level of cardiac output at which the symptoms of congestive failure appear.

The finding that there is no close correlation between the level of the cardiac output and the presence of dyspnea or orthopnea has led to the concept that these symptoms are only indirectly related to the level of the cardiac output.[1] The dyspnea and orthopnea are related to the waterlogging of the lungs, and anything which relieves the edema of the lungs will improve these symptoms even though the cardiac output remains inadequate. Why does waterlogging of the lungs occur in heart failure?

Merrill[13] has shown that an inadequate cardiac output is associated with a reduced renal blood flow and a reduced glomerular filtration rate. This may occur at any level of cardiac output. In patients with heart failure who are exercising and in patients with heart failure with thyrotoxicosis, the cardiac output may be increased above the basal level but still be inadequate for the needs of the body.[14] This will be reflected by a striking reduction in renal blood flow. He believes that in cardiac failure salt and water are retained because the sodium conserving function of the tubules causes them to reabsorb the majority of the reduced amount of sodium presented to them in the glomerular filtrate. Some factor other than sodium retention by the kidney must account for the marked tendency of the cardiac patient to localize the retained fluid in the lungs. It is believed that high pulmonary venous and capillary pressures, due to failure of the left ventricle, account for the fact that so much of the sodium and water retained by the kidney localizes in the lungs and that the dyspnea and orthopnea are symptoms produced by this edema. The waterlogged lungs may be treated by sodium restriction and the use of diuretics. This relieves the symptoms without altering the circulation. They may be treated by increasing the cardiac output by digitalis. This improves the circulation to the kidneys and causes a diuresis. They may be treated by correcting such complications as anemia and hyperthyroidism, thus decreasing the demands of the tissues for blood and making the cardiac output adequate.

SUMMARY AND CONCLUSIONS

1. The cardiac output was measured at rest after a twelve-hour fast in normal subjects and in patients with severe congestive failure. The cardiac output was less than 4.5 liters per minute in 78 per cent of the determinations in patients with failure. It was above 4.5 liters per minute in 82 per cent of the determinations in normal subjects.

2. In two patients with severe anemia and in two patients with hyperthyroidism, the cardiac output was greatly increased above the normal value in the presence of congestive failure. These patients demonstrate that there is no absolute level of cardiac output at which congestive failure develops. The cardiac output was increased, but not to a level adequate for the requirements of the body. Congestive failure occurs whenever the output of the heart is inadequate for the needs of the tissues over a long period of time.

3. Dyspnea and pulmonary congestion are caused by waterlogging of the lungs. The degree of edema in the lungs depends on (a) the height of the pulmonary capillary pressure produced by the left ventricular failure and (b) the amount of salt and water retained by the kidneys. Salt restriction in the diet may lessen

pulmonary congestion without altering the circulation. Because of the many variables involved, there is no close relation between the symptoms of heart failure and the cardiac output.

4. If the cardiac output is measured at rest, the following combinations may be expected to exist:

A. Cardiac output low with failure; remains low with the disappearance of symptoms. Symptoms are relieved by sodium restriction and continued use of diuretics. Majority of patients reported in this paper fall into this classification.

B. Cardiac output low with failure; increases with administration of digitalis or when such complications as pulmonary infarctions clear up. Does not require salt restriction or diuretics when activity is reduced by bed rest.

C. Cardiac output normal with failure; remains normal on compensation. Decompensation develops with increased activity. Cardiac output adequate at rest; symptoms at time of study present because of waterlogging of the lungs which will persist until diuresis is completed.

D. Cardiac output high with failure; falls with compensation. This combination may be shown by (1) restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for mild exertion; and by (2) patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi, and certain infections.

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CONCEALED A-V CONDUCTION: THE EFFECT OF BLOCKED IMPULSES ON THE FORMATION AND CONDUCTION OF SUBSEQUENT IMPULSES

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AN INFREQUENT phenomenon which amplifies the physiology of impulse conduction and impulse formation is the effect of concealed A-V conduction. Under these circumstances, an impulse manifests its effect by altering the transmission or timing of subsequent beats without being manifest electrically itself.

In 1894, Engelmann[1] stated that every effective stimulus applied to the auricle, even if it is not followed by a ventricular response, lengthens the succeeding A-V interval. The actual mechanism to account for this effect was investigated much later. In 1925, Ashman[2] studied the influence of blocked impulses on subsequent conduction in compressed auricular muscle of the turtle heart. He observed that the earlier the blocked impulse follows a transmitted one, the less is its effect upon the conduction time of a subsequently transmitted impulse; and, conversely, the later the blocked impulse follows the transmitted one, the greater is its effect upon subsequent conduction. Drury and Andrus[3] investigated the effects of hydrogen ion concentration upon the muscle of the dog's auricle perfused with Locke's solution, and were able to show that a condition comparable to that termed decrement arises when oxygen-free perfusates of pH 7.0 are used. The condition is one in which an impulse is found to slow down to a halting point in its course through the affected muscle. Similarly, Drury[4] in his observations upon intra-auricular block produced by pressure or cooling stated that "the excitation waves fail to pass through compressed muscle, not because they reach irresponsive muscle, but because they fade away as they travel." In his investigation of 2:1 block, he presented evidence that the alternate (blocked) impulses enter the damaged region and deprive it of the rest period which it obtains when the rate is halved. Lewis and Master[5] in their classical observations upon A-V conduction in the mammalian heart demonstrated clearly that in 2:1 A-V block, whether produced by raising the auricular rate, by stimulating the vagus, or by poisoning with quinidine or the products of asphyxia, the conduction intervals are lengthened by the presence of the alternate auricular beats, that is, those to which the ventricle fails to respond. They defined the "phase of interference" as that period of the cycle during which an impulse which fails to be conducted from auricles to ventricles nevertheless influences the passage

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of the succeeding impulse, postponing or preventing the ventricular response. The phase of interference was found to begin immediately after the period which can be regarded as corresponding to the absolute refractory state of the A-V tissues, and it is operative until conduction from auricles to ventricles occurs. The phase of interference is brief, occupying 0.02 to 0.09 second in the dog's heart. When an auricular impulse falls within this phase, it is conveyed into the conducting tissues but does not traverse them. The impulse so conveyed affects the rest period of those portions of the conducting tissues which the impulse reaches, and in this manner lengthens the next conduction interval. Lewis and Drury,[6] in revising the views of the refractory period, stated that "when the impulse falls early, the response or nonresponse of the A-V tissues is gauged, not by response or nonresponse of the ventricle to that particular impulse, but by the presence or absence of its effect on subsequent conduction."

Concealed conduction in the A-V junction and its influence on subsequent conduction can also be observed in the human heart. The prolongation of the P-R interval after interpolated ventricular premature systoles is the most obvious example of this phenomenon. The retrograde impulse of the ventricular premature systole penetrates into the A-V bundle or A-V node and is stopped before reaching the auricles. The next sinus impulse finds the A-V junction still affected by the retrograde impulse, and this is reflected in the prolonged A-V conduction time of the postextrasystolic beat. Actually, the same mechanism sometimes may be responsible for the complete blocking of the postextrasystolic sinus impulse giving rise to the fully compensatory pause. The region of the A-V junction affected by the retrograde impulse of the ventricular premature systole, rather than the refractory state of the ventricular muscle, may be responsible for the failure of the postextrasystolic sinus impulse to elicit a ventricular response.

Lewis and Oppenheimer[7] demonstrated, in the experimental animal, increase in the grade of partial A-V block following ventricular premature systoles in the absence of retrograde auricular stimulation. Rothberger[8] pointed out that ventricular premature systoles occurring in the presence of auricular fibrillation, particularly bigeminal rhythm after administration of digitalis, tend to be followed by a ventricular pause which is longer than the average interval between two transmitted beats. This can only be explained by inhibition of the A-V conduction by the impulse of the ventricular premature systole, which penetrates in a retrograde fashion into the A-V junction.

In the unusual cases of complete A-V block with retrograde response, it can be demonstrated (Winternitz and Langendorf[9]) that the blocked forward impulses penetrate into the A-V junction and influence the retrograde conduction of the idioventricular beats; only those idioventricular beats which occur in late auricular diastole are followed by retrograde P waves, and the retrograde conduction times vary inversely with the preceding P-R distance. The effect of a blocked impulse on the succeeding conducted impulse is also evident in the unique case of 2:1 A-V block with reciprocal auricular beats, reported by Wolferth and McMillan.[10] Here, the P-R interval of the beat following a blocked sinus impulse is longer than the P-R of the beat following an impulse that was conducted to the auricles in a retrograde fashion. This can be explained by the fact that the period of rest in

the depressed region of the A-V junction is greater when a forward impulse follows a conducted retrograde impulse than when two forward impulses occur in succession, the first of which must have entered the region of block without traversing it. A similar mechanism was assumed by Wolferth[11] to explain an arrhythmia suggesting a supernormal recovery phase. A retrograde impulse which penetrates into the region of A-V block may prevent a simultaneous sinus impulse from penetrating into the same region a little later; thus, the rest period of the critical area is prolonged and this may allow complete conduction of the subsequent sinus impulse.

However, it is conceivable that the effect of blocked impulses upon subsequent conduction may manifest itself not by inhibition but by enhancement, since the existence of a supernormal phase of conduction in damaged tissue has been demonstrated.[12] This may apply to forward conduction following blocked retrograde impulses or to retrograde conduction following blocked forward impulses. Such an explanation was actually offered[13] to account for the occurrence of retrograde conduction in a case of complete A-V block.

Lewis and Master[5] showed that a blocked A-V impulse may not only delay the transmission of the subsequent impulse but may prevent it from reaching the ventricles, so that multiple blockage takes place. Wenckebach and Winterberg[14] considered it likely that the multiple blockage associated with auricular flutter is also an incomplete one in the sense that only the last of the blocked flutter impulses is blocked completely, whereas the others penetrate into the junctional tissues and are stopped before reaching the ventricle. They suggested that such invisible and varying inhibitory effects of the blocked flutter impulses may account for the difficulty, if not impossibility, of analyzing some curves of auricular flutter with a varying ratio of A-V conduction. Kaufmann and Rothberger[15] reported a case of auricular flutter with 2:1 conduction and alternans of A-V conduction. They explained the phenomenon by assuming that the alternate blocked flutter impulse penetrates into a limited portion of the junctional tissues; the varying and alternating conduction times of the conducted impulses can readily be accounted for by the varying distance affected by the alternate blocked impulse, as will be shown in one of our own observations.

Recently, we observed[16] a most unusual case presenting the effect of blocked A-V nodal impulses on subsequent conduction. In a record with frequent nodal premature systoles, there were instances of "dropped beats" without preceding lengthening of P-R, and in one instance, a sudden P-R prolongation of a single sinus beat. Careful analysis of the record revealed that the "dropped beats" were due to interference in the A-V junction of the sinus impulse with the retrograde impulse of a blocked nodal premature systole, and the unexplained P-R prolongation of a single sinus beat was due to a blocked and interpolated nodal premature systole.

Concealed response in the A-V junctional tissues does not only influence subsequent impulse conduction; it may also have an effect on the formation of impulses. In A-V dissociation, where the ventricles are under the control of an A-V nodal pacemaker while the auricles are under the control of the slower S-A node, the sinus impulses occurring at an opportune time are conducted to the ven-

tricles and give rise to early ventricular responses, ventricular capture. These conducted sinus impulses pass through the region of the A-V nodal pacemaker and discharge it, so that the time schedule of the nodal pacemaker is disturbed and its impulse formation starts anew. Instances have been reported[17-23] indicating that under the preceding circumstances the sinus impulse may pass the region of the A-V nodal pacemaker but not reach the ventricles. The blocked sinus impulse penetrates into the A-V junction and before fading out destroys the immature A-V nodal impulse, thus postponing the nodal discharge and causing a disturbance of the ventricular rhythm.

The following four examples are reported to further demonstrate the effect of blocked impulses. Fig. 1 shows a phenomenon which has been observed

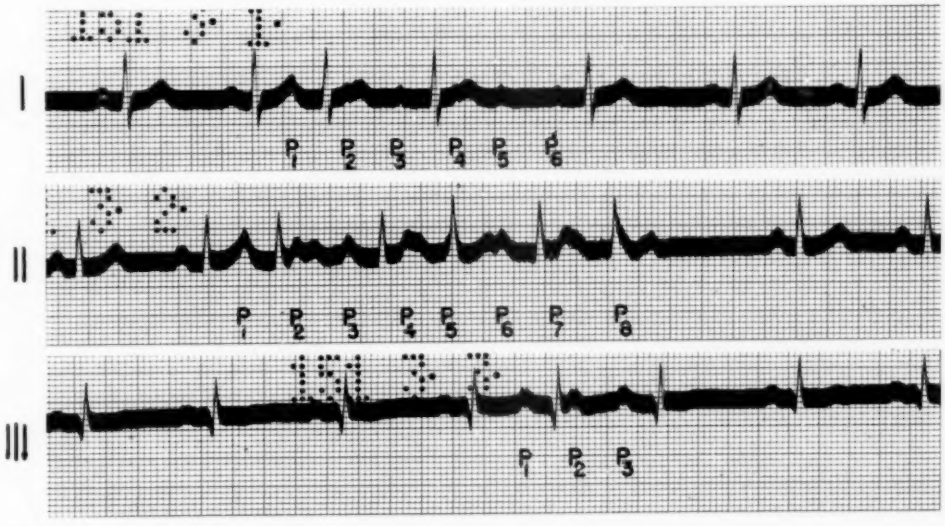

Fig. 1.—Record obtained on a 64-year-old man without signs of cardiac failure. In Lead I, two sinus beats are followed by a run of six auricular premature systoles (P_1-P_6), of which the first, third, and sixth are conducted, whereas the second, fourth, and fifth are not followed by a ventricular complex. P_1 appears on top of T of the second sinus beat and is conducted with a P-R interval of 0.24 second. While P_2, with an R-P of 0.12 second, is blocked, P_4, with a slightly longer R-P (0.13 second), is not only blocked but is followed by another blocked P (P_5). Note that impulse P_5 is blocked, although it occurs much later in diastole than P_1 which was conducted. Impulse P_4 must have penetrated into the junctional tissues and made them refractory when the subsequent impulse (P_5) arrived; this assumption is substantiated by the findings in Lead II. The fact that P-R of the third premature beat is 0.02 second longer than that of the sixth premature beat suggests that the blocked impulse P_2 also affected the A-V junction. In Lead II, after two sinus beats, a run of eight auricular premature systoles (P_1-P_8) occur in succession, the first, third, fourth, sixth, and seventh are followed by a ventricular complex, the second, fifth, and eighth are blocked. Of the conducted ones, P_4 and P_7 occur rather early in diastole, having an R-P of 0.16 second and 0.15 second, respectively. The blocked impulses occur after an R-P of 0.10 second (P_2), 0.03 second (P_5), and 0.03 second (P_8); in this lead the blocked impulses have no demonstrable effect on the P-R of the subsequent beat. In Lead III, after four sinus beats, three premature P waves (P_1-P_3) occur in succession. The middle one, with an R-P of 0.115 second, is blocked but affects the transmission time of the succeeding premature auricular impulse (P_3), which measures 0.24 second as compared with 0.21 second of the preceding one (P_1); the difference of 0.03 second is very significant, considering the fact that P_3 occurs later in diastole than P_1. This case presents a "phase of interference" which follows the actual absolute refractory phase and precedes the period during which impulses are followed by a ventricular response. The short strips do not allow an accurate determination of the duration of the phase of interference. It begins, at most, 0.115 second after the start of QRS and it ends at least 0.13 second after QRS, thus lasting for at least 0.015 second.

before.[14,24] When two auricular premature systoles occur in succession, the first of which is "blocked," the blocked auricular impulse may give rise to undue prolongation of the P-R of the subsequent auricular premature systole or may actually be responsible for a failure of the ventricles to respond to the second premature impulse, so that two blocked auricular premature systoles occur in succession.

Fig. 2 shows a second degree A-V block varying between 2:1, 3:2, and 4:2. All ventricular beats in Leads I and II are considered to be conducted, since Lead III shows a ventricular pause which is considerably longer than any pause in Leads I or II. Some of the conducted P waves occurring late in ventricular diastole are transmitted with a P-R shorter than that of other beats occurring earlier in diastole (compare P_3-R_3 of Cycle 3 with that of Cycle 4 in Lead I). This can be explained by the effect on subsequent conduction of a blocked impulse belonging to the P wave partly hidden in the preceding QRS complex. The assumption that such early auricular impulses actually penetrate into the A-V junction without reaching the ventricles is substantiated by the occurrence in the same record of a ventricular response to impulses falling only 0.01 second later in the ventricular cycle (namely, Lead II, Cycle 4). On one occasion such a blocked but almost conducted impulse not only postponed the transmission of the succeeding impulse but actually prevented it, so that a double blockage occurred (namely, Lead III, Cycle 6). The disturbance of impulse conduction observed in this patient is analogous to that produced by Lewis and Master[5] in the dog's heart by "shifting the middle (blocked) auricular beat" in 2:1 A-V block, so that the middle P occupies a different position in the cycle, preceding, falling into, or occurring after the "phase of interference." Tables I and II demonstrate the effect of the blocked impulses (P_2) on the transmission time (P_3-R_3) of the subsequent impulses (P_3). It can be seen that this effect is dependent on the duration of R_1-P_2 which indicates the time at which the impulse of P_2 falls in the cardiac cycle. With R_1-P_2 measuring 0.06 to 0.15 second, P_3-R_3 measures 0.39 to 0.41 second; with R_1-P_2 measuring 0.16 second, P_3-R_3 increases abruptly to 0.46 to 0.48 second; and with R_1-P_2 measuring 0.17 second or more, P_2 is followed by R_2 (with one exception which will be discussed) and P_3-R_3 rises to infinity, the auricular impulse (P_3) failing to reach the ventricles. On one occasion (Lead III, Cycle 6), with a R_1-P_2 of 0.18 second, block occurs for two P waves (P_2 and P_3) in succession. P_1-R_1 of Cycle 7 is short (0.40 second), indicating that it was not influenced by the preceding impulse (P_3 of Cycle 6) although the latter occurred very late in the cycle; this in turn proves that the impulse P_2 of Cycle 6 was responsible for the blockage of P_3 of this cycle. In this instance, the delaying effect of a blocked impulse is so great as to equal that of a conducted one, thus causing actual blockage of the subsequent impulse.

Fig. 3 is similar to the case of Kaufmann and Rothberger[15] mentioned previously; it shows a case of auricular flutter with 2:1 A-V conduction and an alternans in the spacing of R-R. The diagram of Lead I, Fig. 2, which applies to the same mechanism in a case of sinus rhythm with 2:1 A-V block, illustrates how such pseudoalternans of the A-V conduction can be explained by the effect of the

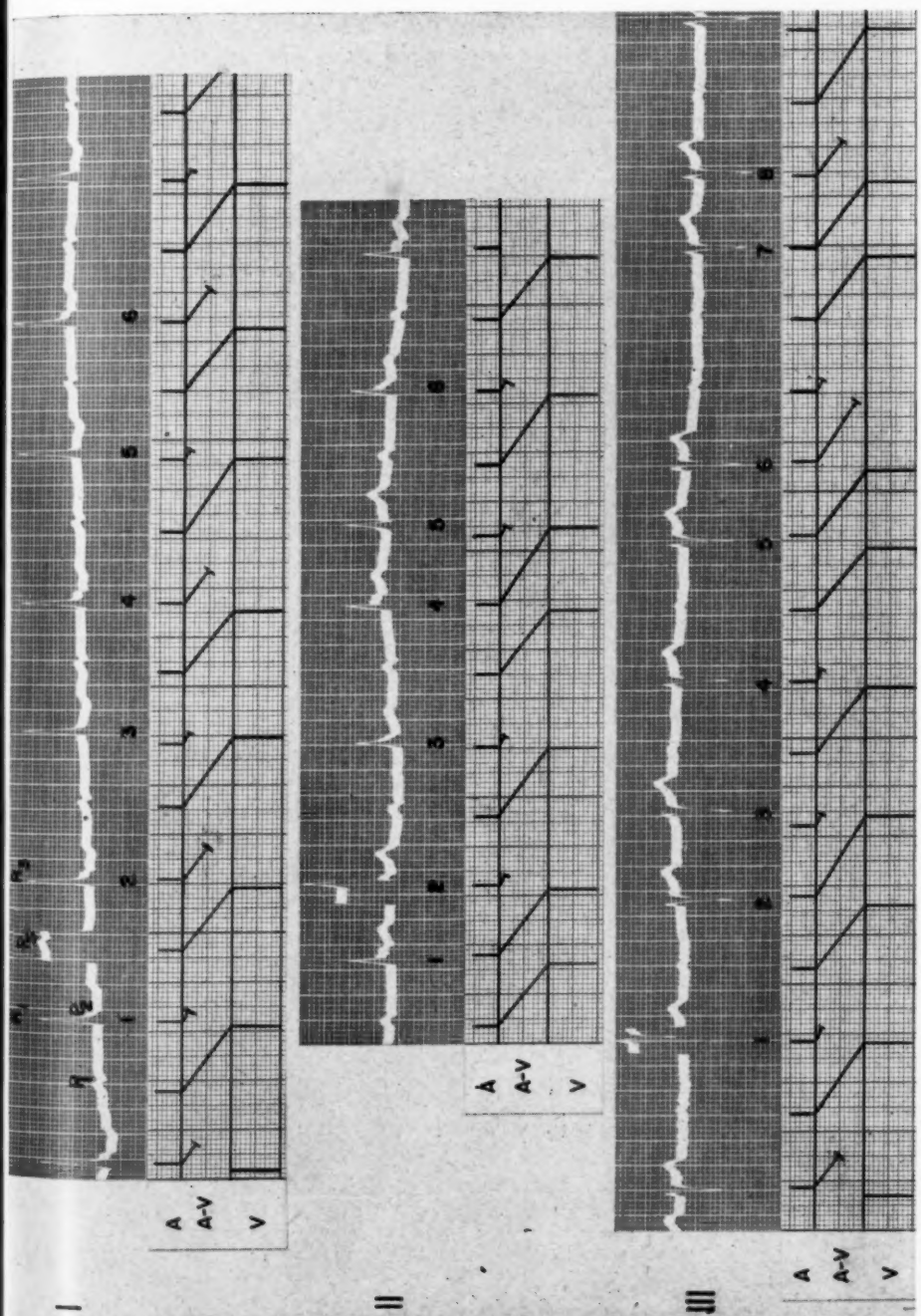

Fig. 2.—This record was taken on a 53-year-old man with subacute bacterial endocarditis superimposed on an old endocarditis of the rheumatic type involving the aortic valve. Autopsy, performed three days after this record was taken, revealed an erosive mycotic aneurysm involving both the interauricular and interventricular septa. The mechanism of the conduction disturbance is illustrated in the diagram below the electrocardiogram. The conventions are those used customarily. *A-V* represents the spread of the impulse through the A-V junction between the auricles (*A*) and the ventricles (*V*). Blockage of an impulse is indicated by short lines at right angles to the oblique lines representing the impulse spread; varying length of the oblique lines representing blocked impulses indicates the varying distance to which the blocked impulses penetrate into the A-V junction. The numerals beneath the QRS represent the beginning of the cycles of beats referred to. In Lead I the P waves and R waves pertaining to a cycle are labelled P_1, P_2, P_3, R_1, and R_2, respectively. Discussed in text.

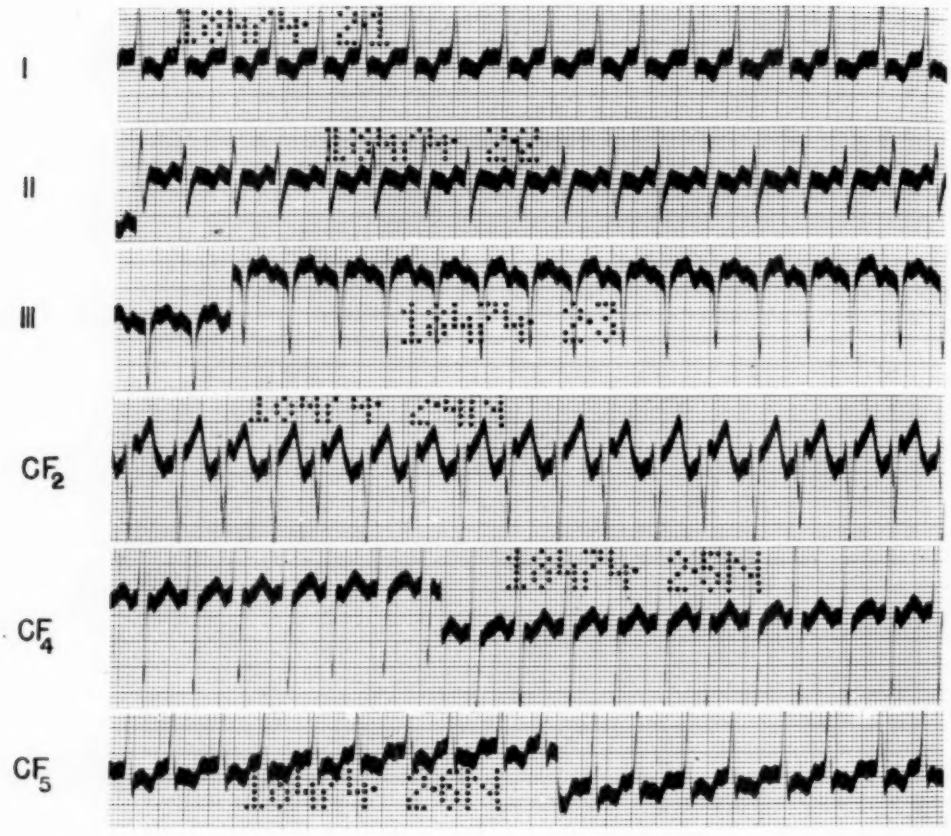

Fig. 3.—Auricular flutter with 2:1 A-V conduction. The flutter waves occurring at a rate of 316 per minute are clearly seen in Leads II, III, CF_2, and CF_4. The ventricular rate shows a regular irregularity, in that a long R-R alternates with a short R-R, the difference measuring 0.03 to 0.04 second; this is easily recognized by comparing the intervals between the R waves and the preceding F waves, or the intervals between the R waves and the subsequent F waves. The alternation in contour of the ventricular complexes can be accounted for in part by different superimposition of QRS-T and the F wave. The alternation in length of the F-R intervals of the conducted flutter impuses can be explained by the alternating effect of the blocked flutter impulses (compare with the identical mechanism in Fig. 2, Lead I).

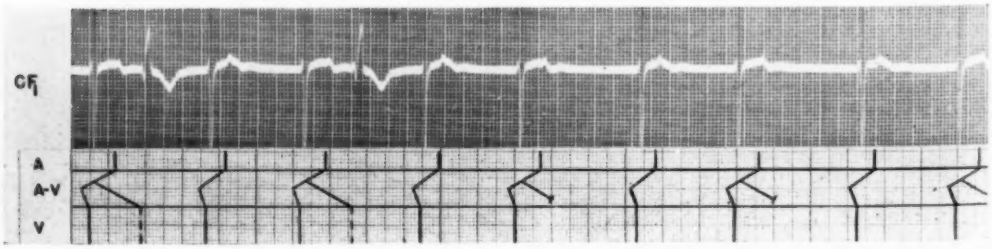

Fig. 4.—Conventions as in Fig. 2. The reciprocal beats showing aberrant ventricular conduction are represented by dashed lines. Discussed in text.

alternate blocked auricular impulse which penetrates into the junctional tissue. It cannot be determined whether all blocked flutter waves fall in the "phase of interference," with the one occurring later in the cycle exerting the more marked

TABLE I. MEASUREMENTS OF THE RECORD ILLUSTRATED IN FIG. 3*

LEAD	CYCLE	P_1-R_1	R_1-P_2	P_2-R_2	P_2-P_3	P_3-R_3	R_1-P_3
I	1	44	13	∞	56	40	69
	2	40	16	∞	57	48	73
	3	48	6	∞	56	40	62
	4	40	16	∞	57	48	73
	5	48	10	∞	56	40	66
	6	40	16	∞	56	46	72.5
II	1	38.5	18	44	56	∞	
	2	44	12	∞	56	41	68
	3	41	13.5	∞	58	40	71.5
	4	40	17	50	60	∞	
	5	50	6	∞	56	41	62
	6	41	15	∞	56	40	71
III	1	46	13	∞	56	40	69
	2	40	19	50	58	∞	
	3	50	8	∞	56	41	64
	4	41	15	∞	58	39	73
	5	39	20	44	58	∞	
	6	44	18	∞	60	∞	8
	7	40	19	44	60	∞	
	8	44	16	∞	60	48	74

*The end of P was easier to determine than its beginning; for that reason, in the above figure, P stands for the end of P and R for the beginning of QRS. All measurements are in hundredths of a second. Discussed in text.

TABLE II. MEASUREMENTS OF TABLE I ARRANGED IN ORDER OF INCREASING DURATION OF R_1-P_2 TO DEMONSTRATE THE INFLUENCE OF THE POSITION OF P_2 ON P_3-R_3

R_1-P_2	P_2-R_2	P_3-R_3
6	∞	40
6	∞	41
8	∞	41
10	∞	40
12	∞	41
13	∞	40
13	∞	40
13.5	∞	40
15	∞	40
15	∞	39
16	∞	48
16	∞	48
16	∞	48
16	∞	46
17	50	∞
18	44	∞
18	∞	∞
19	44	∞
19	50	∞
20	44	∞

influence upon subsequent conduction; or whether only those of the blocked flutter impulses which fall late in diastole occur during the "phase of interference," whereas those occurring early in the ventricular cycle fall into the "actual" absolute refractory phase and have no effect on the "F-R" of the succeeding beat.

Fig. 4 shows an example of disturbed impulse formation due to a mechanism which to our knowledge has not been reported before. The patient on whom the record was obtained was a 76-year-old woman with arteriosclerotic heart disease and congestive heart failure who developed the illustrated arrhythmia after digitalization. The record (Lead CF_1) shows the whole heart to be under the control of the A-V node; all nodal beats are followed by a retrograde P wave. The retrograde contour of P was clearly evident by comparing the P wave pattern in the limb leads with that observed at the time of sinus rhythm. The retrograde conduction times in Fig. 4 alternate in length, measuring 0.28 second and 0.20 second; the R-R distances between the nodal beats also alternate in length, measuring 1.26 to 1.31 seconds and 1.00 to 1.05 seconds. The explanation for the latter phenomenon is given by the first portion of the record which shows on two occasions another ventricular complex following the longer retrograde conduction. This beat represents a reciprocal beat with aberrant ventricular conduction, and the long ventricular pauses in the second portion of the record are due to the occurrence of blocked reciprocal beats. The reciprocal impulse passes the nodal pacemaker, but is blocked below it before reaching the ventricles. The premature discharge of the nodal pacemaker is responsible for the lengthening of the alternate R-R intervals. The R-R intervals containing a reciprocal beat are almost identical in duration with the long R-R intervals without a reciprocal beat, the latter actually containing a blocked reciprocal beat. For the sake of simplicity, it is assumed in the diagram to Fig. 4 that the time for forward conduction of the A-V nodal beats remains constant; actually, it may be slowed after the transmission of a reciprocal beat[25,26] with the consequence that (a) the apparent improvement of the retrograde conduction time in the beat following a reciprocal impulse may partly be due to a delay in forward conduction, and (b) the cycle length of the A-V nodal pacemaker may be longer than the short R-R interval of two successive nodal beats seems to indicate.

SUMMARY AND CONCLUSIONS

1. The spread of an impulse which affects the A-V junction by penetrating into it without traversing it, thus failing to reach the auricles or ventricles (depending on the direction in which the impulse travels), finds no direct expression in the electrocardiogram. Indirect evidence for such concealed A-V conduction is the influence of the blocked impulse on the transmission time or on the formation of a subsequent impulse.

2. The literature dealing with the effect of blocked impulses on conduction and formation of subsequent impulses is reviewed.

(a) The simplest example of the effect of a blocked impulse is the post-extrasystolic P-R prolongation due to blocked retrograde conduction after an interpolated ventricular premature systole.

(b) Similarly, the failure of the sinus impulse following a ventricular premature systole to elicit a ventricular response may be due, in some instances, to the inability of the A-V junctional tissues to transmit the impulse after it has been affected by the blocked retrograde impulse of the ventricular premature systole, and not to refractoriness of the ventricular muscle.

(c) The pause after ventricular premature systoles in the presence of auricular fibrillation indicates that a retrograde impulse has affected the junctional tissues.

(d) The increase in the grade of a partial A-V block following ventricular premature systoles, even if they are not followed by a retrograde P, demonstrates the effect of blocked retrograde impulses.

(e) Cases of complete forward block in the A-V junction and preserved retrograde reponse show the effect of the blocked forward impulse on subsequent retrograde conduction.

(f) A blocked retrograde impulse, by reaching a depressed area in the A-V junction prematurely, may prolong the period of rest in that area and thus shorten the conduction time of the subsequent forward impulse.

(g) It is conceivable that, in depressed cardiac muscle, an impulse falling into the supernormal phase of a preceding blocked impulse may be conducted faster instead of being delayed by the effect of the blocked impulse.

(h) Multiple blockage may occur as a result of a blocked impulse which was partially conducted and which influenced the subsequent impulse in the same way as a completely conducted one; such a mechanism is probably common in auricular flutter.

(i) A blocked A-V nodal premature systole may account for a "dropped beat," and a blocked and interpolated nodal premature systole can give rise to an apparently unexplained P-R prolongation of a single beat.

(j) In cases of A-V dissociation, some of the impulses of the slower pacemaker (S-A node), after passing and discharging the faster A-V nodal pacemaker, may be stopped below the latter before reaching the ventricles. The result of such concealed A-V conduction is a disturbance in the impulse formation of the nodal pacemaker.

3. Three new instances demonstrating the effect of blocked A-V impulses on succeeding impulse conduction and one showing the influence on subsequent impulse formation are reported and illustrated. They demonstrate: (a) the effect of a blocked auricular premature systole on A-V conduction of a subsequent auricular premature systole from the same focus; (b) the effect of the blocked auricular impulses on subsequent A-V conduction in a case of 2:1 A-V block, depending on the exact position of the blocked P wave in the cardiac cycle, and confirm the existence of a "phase of interference" and explain the transition from one grade of block to another; (c) the effect of the blocked flutter impulses in a case of auricular flutter with 2:1 A-V conduction giving rise to a pseudo-alternans of A-V conduction; and (d) a hitherto unreported disturbance of impulse formation, namely, discharge of the A-V nodal pacemaker by blocked reciprocal beats.

4. These observations support the view that concealed A-V conduction may account for the difficulty in analyzing some curves of auricular flutter with a varying ratio of A-V conduction. The same phenomenon may also explain some of the discrepancies encountered in the construction of recovery curves of A-V conduction in cases of partial A-V block based on simple correlation of P-R and R-P.

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THE BEHAVIOR OF THE VENOUS PRESSURE DURING VARIOUS STAGES OF CHRONIC CONGESTIVE HEART FAILURE

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THE explanation of the pathologic physiology of congestive heart failure is today, as ever, a perplexing problem in medicine. Opinion has shifted from one theory to another as various investigators have brought forth additional data and propounded new ideas. The two basic explanations have been termed the forward failure theory and the backward failure theory of chronic congestive heart failure. The former may briefly be stated as follows: the pathology causing the clinical picture of congestive heart failure occurs in the organs supplied by the failing chambers of the heart and is due to a decrease in the blood flow through these organs. The latter theory holds that the pathology leading to the clinical picture of congestive heart failure occurs in the tissues feeding blood to the failing (enlarged) chambers of the heart, the essential phenomenon being an increase in the intracapillary pressure in these tissues.

Although the principles of the backward failure theory were well enumerated over one hundred years ago,[1] it did not become generally accepted until the last decade when it was again brought to attention.[2] In the interim, the majority of observers were advocates of the forward failure theory,[3-6] and as recently as 1933 it was the more widely accepted of the two theories.[7] For the past several years the backward failure theory has been generally accepted, but more recent investigations have brought forth data which are difficult to explain in the light of this theory. These data include (1) the absence of edema in the lower extremities after ligation of the inferior vena cava, despite extremely high venous pressures in these limbs,[8] (2) the failure of the venous pressure to show a rise after severe damage to the right ventricle in dogs,[9] and (3) the finding of a gain in weight and an increase in plasma volume before the venous pressure reaches abnormal levels following administration of salt to compensated cardiac patients.[10] These and other facts which are difficult to explain by either the forward or backward failure theory have been discussed.[11] Other possible explanations involving sodium metabolism[12-14] and the role of the kidney[10,11] in congestive heart failure have been suggested, as well as the action of hormones[15] involving either the kidney[16] or the liver[17] and sodium metabolism.

This study was undertaken because of the lack of adequate data showing the day-to-day behavior of the venous pressure in congestive heart failure, and

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to ascertain, as accurately as possible, the relation of the venous pressure to the state of the congestive heart failure.

METHODS AND MATERIALS

Patients.—Twenty-three Negro patients who entered the hospital in congestive heart failure (all in Functional Class IV) were observed. Of these, eight were women and fifteen, men. Their ages varied from 19 to 66 years. The causes of their heart disease were: hypertension, 13 patients; syphilis, 6; senile arteriosclerosis, 3; and rheumatic fever, 1 patient. No attempt was made to influence the therapy. The regular hospital regimen for congestive heart failure was employed in all patients. Two of the patients died while being studied, one (Number 2) of a coronary occlusion and the other (Number 20) of uremia due to an associated chronic glomerulonephritis. Multiple episodes of decompensation and recovery were observed in four patients (Numbers 7, 8, 9, and 12) during their hospital stay. On three occasions, decompensation was brought about by the administration of 12 Gm. of sodium chloride per day. A total of thirty-four significant changes in the state of congestive heart failure, as evidenced by weight gain or loss, were observed. Pertinent data concerning the patients are summarized in Table I.

TABLE I. PERTINENT DATA ON PATIENTS STUDIED

SUBJECT NUMBER	SEX	AGE	DIAGNOSIS*	DURATION OF HEART DISEASE	NUMBER OF EPISODES OF CHF	TIME SINCE LAST FAILURE	TREATMENT RECEIVED†
1	F	50	HCVD	12 yr.	2	6 mo.	1, 2, 3, 4
2	F	50	LHD	9 mo.	1		1
3	M	42	HCVD	2 mo.	1		1, 2
4	M	53	HCVD	1 wk.	1		1, 2
5	F	51	ASHD	3 mo.	1		1, 2
6	M	29	HCVD	3 wk.	1		1, 4
7	M	62	ASHD	2 mo.	1		1, 3
8	M	46	LHD	14 mo.	2	9 mo.	1, 2, 3
9	F	35	HCVD	2 yr.	3	3 mo.	1, 2, 3, 4
10	M	66	LHD	2 mo.	1		1
11	M	60	ASHD	5 yr.	9	6 mo.	1, 3
12	M	59	LHD	3 mo.	1		1, 2, 3, 4
13	M	49	LHD	2 yr.	1		1, 2, 3
14	M	55	HCVD	2 yr.	2	2 yr.	1
15	F	48	LHD	5 wk.	1		1, 2, 3, 4
16	M	43	HCVD	2 mo.	1		1, 3
17	M	40	HCVD	6 wk.	1		1, 3
18	M	56	HCVD	3 wk.	1		1, 3
19	M	19	RhHD	6 yr.	11	6 mo.	1, 2
20	F	52	HCVD	2 wk.	1		1
21	M	52	HCVD		1		1, 2
22	F	54	HCVD	2 mo.	1		1, 3
23	F	47	HCVD	4 yr.	4	3 mo.	1, 2, 3

*HCVD—Hypertensive cardiovascular disease
LHD—Syphilitic heart disease
ASHD—Arteriosclerotic heart disease
RhHD—Rheumatic heart disease
†1—Low sodium diet (1.6 Gm. NaCl/day) with fluids ad lib
2—Digitalis
3—Mercurial diuretic
4—Ammonium chloride

Venous Pressure.—Serial determinations of the venous pressure demanding daily venepunctures for as long as two months in some cases were made feasible by the Phlebomanometer, a method of direct measurement of venous pressure.[18] This method has been described in the literature[15] but will be briefly discussed. The normal range for the venous pressure in the antecubital vein by this method is 50 to 140 mm. H_2O; the normal variations for other veins have been presented elsewhere.[18] The heart level or reference point, termed the phlebostatic level, is a horizontal plane passing through the phlebostatic axis. This axis is defined as the intersection of a frontal plane lying midway between the anterior and posterior surfaces of the thorax, measured at the xiphisternal junction, and a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. Indelible crosses were made on both sides of the thorax marking the phlebostatic axis so as to achieve a constant reference level for serial determinations. The patient was placed in the same position each day during the study. A carpenter's level on a long rod was employed to insure the position of the vein at the phlebostatic level. Since this method depends on an equalization of pressures[18] rather than on a flow of fluid[20,21] to achieve equilibrium, the needle used may be of small diameter (No. 22 and No. 24 gauge). The venous pressure in several superficial veins was determined each day on all patients to serve as a check on the values obtained, as well as to show the behavior of the venous pressure in the various parts of the body during various stages of congestive heart failure. All of the precautions previously described[18] were heeded. The range of error of this method as employed was ± 5 mm. of water.

The procedure involved the following: (1) The phlebostatic axis was determined. (2) The vein to be used was placed at the phlebostatic level. (3) Two per cent citrate was drawn into the needle and adaptor so that the fluid level was visible. (4) The needle was inserted into the vein and its pressure quickly equalized by compression of the rubber bulb of the phlebomanometer. Equalization of pressures resulted in a fluid level which was motionless except for the oscillations of venous pulse with respiration. To keep the fluid level constant, the pressure in the rubber bulb was gradually decreased since the venous pressure dropped about 20 mm. H_2O in the first three to four minutes following venepuncture. (5) Four minutes after insertion of the needle, the venous pressure was read from the scale of the manometer. (6) The position of the vein was rechecked with the carpenter's level.

Weight.—Weight was selected as the most accurate practical index of the fluid content of the body. As such, it was considered a good criterion of the state of the congestive failure. The graphs presented, therefore, show the chronological relation of the changes in weight to the alterations in venous pressure as the patient improved or became more decompensated.

A platform type scale was used which was accurate to one-fourth pound. The patients were weighed daily at 10:00 A.M. to give a constant relation to meals and, in so far as possible, to bowel function. The patients were asked to void just prior to being weighed and only the hospital gown was worn. The initial

position of the lever arm was checked before each weighing and two determinations of each weight were taken.

The majority of the initial studies on the patients recovering from congestive heart failure were done at the time of admission to the wards and all were begun within twelve hours after entering the hospital. None had received specific therapy prior to the initial determinations of weight and venous pressure. The patients who showed a change for the worse had all been under observation (daily weight and venous pressure) prior to the reversal. The venous pressures graphed represent values obtained daily in the antecubital vein, although pressures in multiple veins were taken each day. The antecubital vein was chosen because it is technically the best suited for the purpose, being large and superficial. In addition, the chance of error due to spasm of this vein is minimal, and the antecubital space is least painful of all areas presenting a superficial vein for venepuncture. Any change in venous pressure or weight exceeding the range of error for the methods employed was considered an actual change. Because the relative importance of small variations in weight and venous pressure could not be evaluated, the rates at which the total changes in weight and venous pressure were achieved were determined by the method that will be described.

RESULTS

Significant changes in the degree of congestive heart failure were encountered thirty-four times. The chronological relationship of the rise or fall in venous pressure to the change in weight was noted (Table II, *A*). These data were further divided, depending on whether or not the patient was becoming more or less congested (Table II, *B*).

TABLE II. RELATIONSHIPS OF CHANGE IN VENOUS PRESSURE TO CHANGE IN BODY WEIGHT

A. Chronological Relationship of Venous Pressure to Weight in Thirty-four Instances of Change of State of Congestive Heart Failure	
1. Simultaneous change in weight and venous pressure	20 (59%)
2. Venous pressure change preceding the change in weight	8 (24%)
3. Weight change preceding the change in venous pressure	6 (17%)
B. Chronological Relationship of Venous Pressure to Weight in Twenty-six Patients Recovering from Congestive Heart Failure and in Eight Patients Decompensating	
1. *Recovering*	
Group 1. Simultaneous weight and venous pressure decrease	16 (62%)
Group 2. Venous pressure decrease preceding drop in weight	6 (23%)
Group 3. Weight drop preceding decrease in venous pressure	4 (15%)
2. *Decompensating*	
Group 4. Simultaneous weight and venous pressure increase	4 (50%)
Group 5. Venous pressure increase preceding weight increase	2 (25%)
Group 6. Weight increase preceding venous pressure rise	2 (25%)

Composite graphs of the daily changes in the weight and venous pressure observed in the patients of the six groups (Table II, *B*) are given (Figs. 1, 2, 3, 4, 5, and 6). In addition, for each of the thirty-four significant changes in the state of congestion, the total change in venous pressure and weight was noted, as well as the time in days required for each total change to be achieved. The per cent of the total change that was achieved each day was calculated. Composite graphs of these values could not be made directly without distorting the relation of weight to venous pressure since some patients achieved their total change in three days while others required ten days and longer. For this reason, the duration of each significant change was noted and divided into fifths. The per cent of total change achieved during each fifth of total duration of change was computed (small graphs in Figs. 1, 2, 3, 4, 5, and 6).

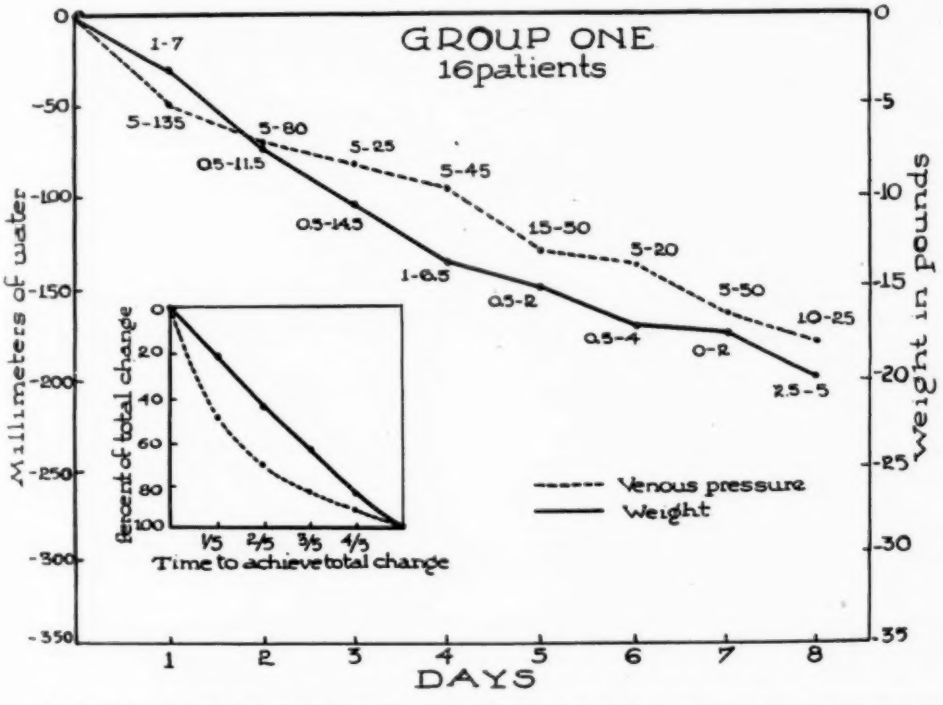

Fig. 1.—A composite graph showing the time relation of changes in venous pressure to weight in sixteen patients recovering from congestive heart failure. There were no independent decreases of weight or venous pressure in these patients. The small graph represents the average per cent of total change in weight and venous pressure that was achieved during each one-fifth of the time necessary to accomplish the total change (see text). In this, and in all graphs to follow, the values indicated near the points (mean values) in the curves are the extremes for the group.

Patients Recovering From Congestive Heart Failure.—Twenty-six instances of recovery from congestive heart failure were observed (Table II, *B*). In sixteen of these, the weight and venous pressure at the end of the first hospital day had decreased from the values obtained on admission (Fig. 1). The average weight loss over this period was 3.0 pounds (range, 1.0 to 7.0 pounds) and the mean

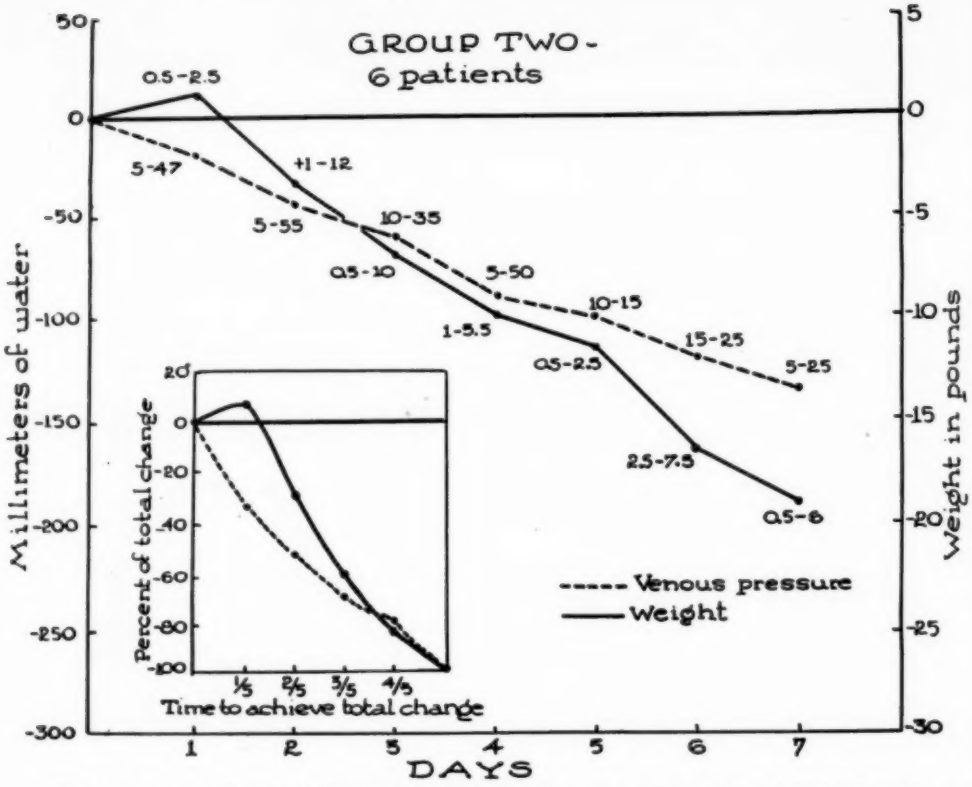

Fig. 2.—A composite graph showing the behavior of venous pressure and weight in six patients recovering from congestive heart failure. In these patients the venous pressure decreased from 5 to 47 mm. H_2O prior to the initial decrease in weight. The small graph shows the per cent of total change achieved during each one-fifth of time of total change. The venous pressure began to fall first, but weight finally fell at a faster rate.

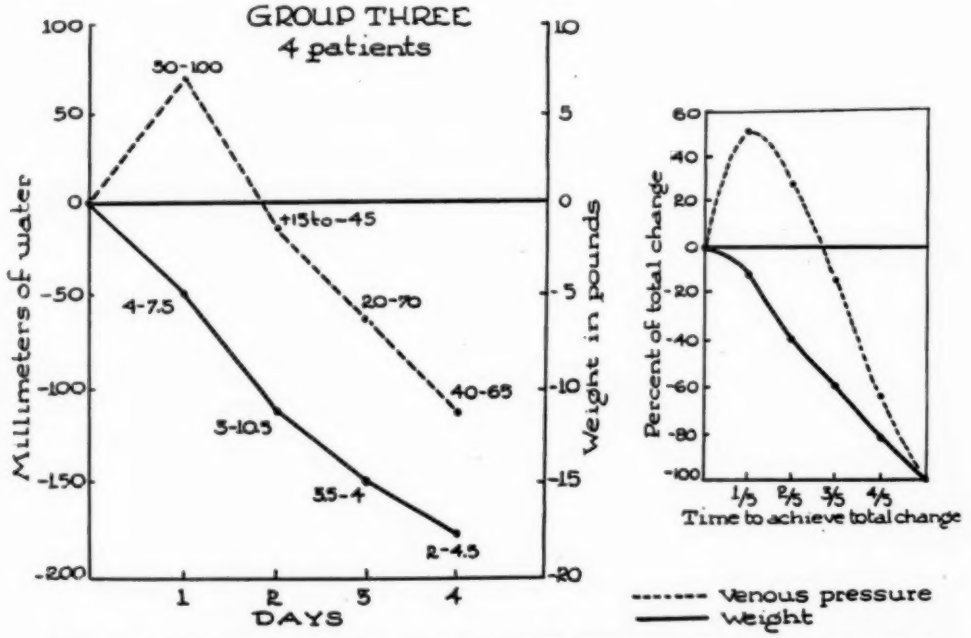

Fig. 3.—A composite graph of four patients recovering from congestive heart failure. The relation of weight loss to venous pressure change is noted. The weight began to fall prior to the venous pressure decrease. The small graph shows the per cent of total change achieved during each one-fifth of time of total change. The weight began decreasing first, but the venous pressure finally fell at a faster rate.

venous pressure decrease was 49 mm. H_2O (extremes, 5 mm. H_2O and 135 mm. H_2O). Although both the venous pressure and weight decreased each day in these sixteen patients (Fig. 1, large graph), the venous pressure achieved its total change at a faster rate initially than did the weight (Fig. 1, small graph).

In six of the twenty-six patients recovering from congestive heart failure, the weight had risen from 0.5 to 2.5 pounds above the initial level after one hospital day (Fig. 2). In this period the venous pressure had dropped 5 to 47 mm. of water. In two patients there was a further increase in weight on the second hospital day despite a continued fall of venous pressure. By the third day, the weight of all six patients had begun to fall but only subsequent to an average decrease in venous pressure of 45 mm. of water. The venous pressure achieved its total decrease at a faster rate initially than did the weight (Fig. 2, small graph).

In four of the twenty-six patients recovering from congestive heart failure, the venous pressure had risen after one hospital day from 50 to 100 mm. H_2O above the initial value (Fig. 3), while the weight had decreased from 4.0 to 7.5 pounds.

Patients Becoming More Congested.—Eight patients were observed as their congestive heart failure became worse (Table II, *B*, *2*). Four of these changes occurred in patients with advanced heart disease who, despite therapy, had not completely recovered from a previous episode of congestive heart failure. Three decompensation trends were brought about by administration of 12 Gm. of sodium chloride per day to patients who were not in congestive heart failure. One patient changed from the compensated to the decompensated state despite therapy which included a low sodium diet.

Of the four patients suffering reversals while recovering from congestive heart failure, two showed a weight gain prior to a venous pressure rise (Fig. 6), one showed a venous pressure rise prior to a weight gain (Fig. 5), and one showed a simultaneous rise in both (Fig. 4).

Of the three patients who were given salt, two showed a simultaneous rise in weight and venous pressure (Fig. 4) and one had a rise in venous pressure prior to a weight gain (Fig. 5). The other patient whose venous pressure was normal when decompensation began showed a simultaneous rise in weight and venous pressure while on a low sodium diet.

Patients Showing Changes in Either Weight or Venous Pressure Prior to a Change in the Other.—The patients in Groups 2, 3, 5, and 6 (Table II, *B*) underwent changes in their state of failure which were characterized by an initial alteration of either weight or venous pressure, but not of both simultaneously. These independent changes are listed (Table III) and the percentage of the total change in weight or venous pressure which they represent is shown. Comparing Groups 2 and 3, patients recovering from congestive heart failure in whom there was not a simultaneous decrease in weight and venous pressure, we see that there is no significant difference in the percentage of the total venous pressure decrease (Group 2) and the percentage of the total weight fall (Group 3) that were achieved

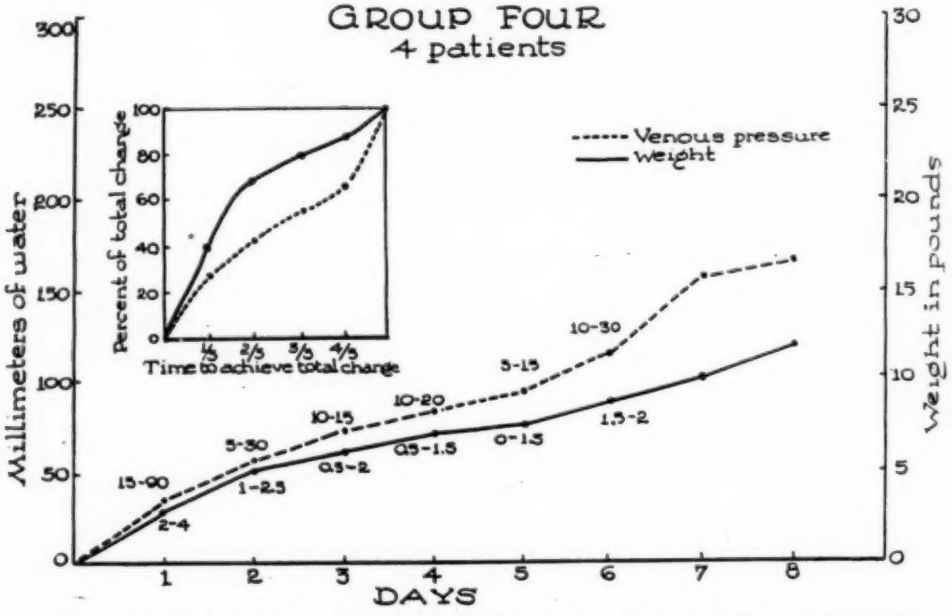

Fig. 4.—A composite graph of four patients developing congestive heart failure. Of these, three had normal venous pressures initially. Two of these three patients received sodium chloride (12 Gm. per day). Both the weight and venous pressure showed a rise each day. The small graph shows the average per cent of total rise in weigh tand venous pressure achieved during each one-fifth of total duration of the congestive process. Initially, the weight rose faster than the venous pressure; later, the reverse was true.

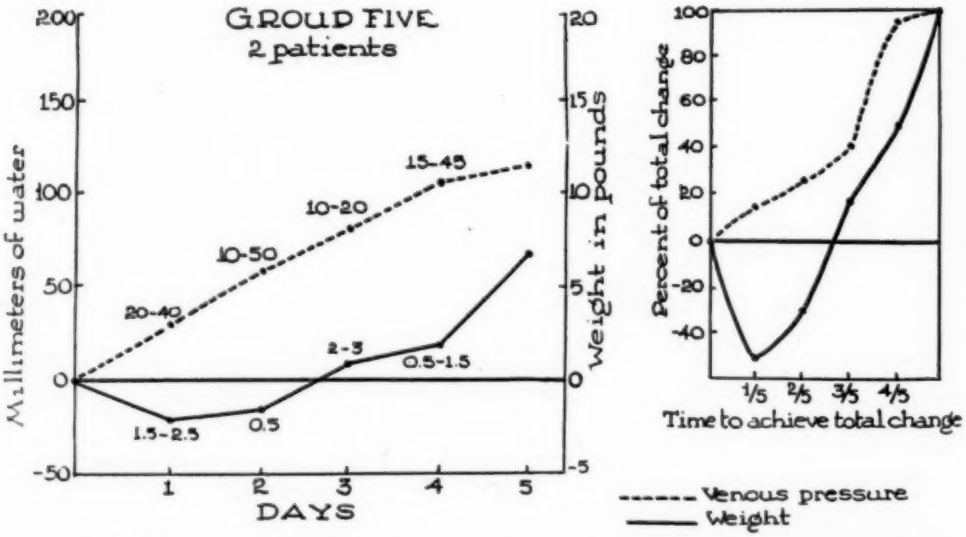

Fig. 5.—The average change in weight and venous pressure for two patients decompensating. One had a normal venous pressure initially and was given 12 Gm. sodium chloride daily. The relation of venous pressure rise to weight gain is shown. The venous pressure rose from 20 to 40 mm. H_2O before the weight began increasing. The small graph represents the per cent of total rise in weight and venous pressure achieved during each one-fifth of the total time of study. The venous pressure began rising although the weight fell. After the weight had achieved 15 per cent of its total rise, the rate of venous pressure rise increased.

independently of the other (compare 44 per cent with 37 per cent). The same may be said of the patients developing more failure (Groups 5 and 6) in whom there was not a simultaneous rise in weight and venous pressure (compare 27 per cent with 22 per cent).

TABLE III. PATIENTS SHOWING A CHANGE IN ONE FACTOR PRIOR TO A CHANGE IN THE OTHER. THE VALUES OF THE INDEPENDENT CHANGES AND THE PER CENT OF THE TOTAL CHANGE WHICH THESE REPRESENT ARE GIVEN

Recovering

Group 2			Group 3		
1	20 mm. H_2O	13%	1	3 lbs.	20%
2	25 mm. H_2O	42%	2	7½ lbs.	75%
3	45 mm. H_2O	50%	3	4 lbs.	30%
4	60 mm. H_2O	75%	4	4½ lbs.	21%
5	25 mm. H_2O	36%			
6	25 mm. H_2O	46%	Avg.	4.9 lbs.	37%
Avg.	33 mm. H_2O	44%			

Developing Failure

Group 5			Group 6		
1	40 mm. H_2O	32%	1	2 lbs.	18%
2	20 mm. H_2O	21%	2	2 lbs.	25%
Avg.	30 mm. H_2O	27%	Avg.	2 lbs.	22%

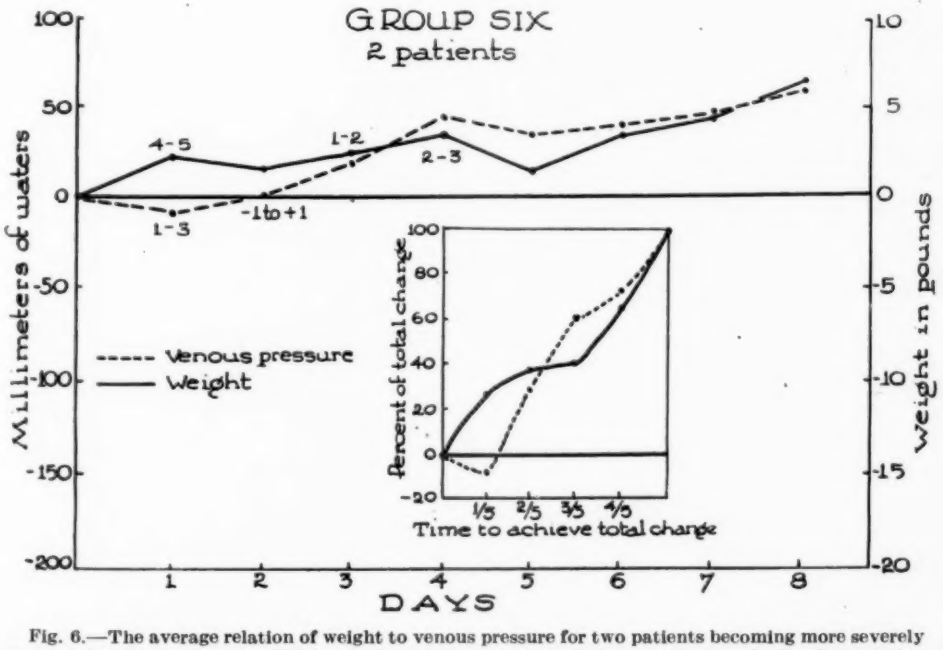

Fig. 6.—The average relation of weight to venous pressure for two patients becoming more severely congested despite treatment. Neither had completely recovered from a recent episode of congestive heart failure when this reversal occurred. Initially, a weight gain preceded the rise in venous pressure. The small graph shows the per cent of total rise in venous pressure and weight achieved during each one-fifth of the congestive process. A rapid rate of venous pressure increase followed the initial rise in weight.

DISCUSSION

In the majority of the patients observed, the behavior of the venous pressure was like that generally reported for patients with cardiac disease.[22-30] It was in the normal range when the patients were compensated, rising as the picture of congestive heart failure developed; it was elevated in marked failure, decreasing as recovery progressed, and was normal again when compensation had returned. This confirms the importance of venous pressure determinations in establishing the diagnosis of cardiac decompensation and in evaluating the efficacy of therapy and the progress of the disease. It also indicates the inability to discern impending congestive failure or diminished myocardial reserve in the compensated patient by this procedure.[29,30]

In some patients admitted in congestive failure, the initial venous pressure was in the normal range despite the presence of signs and symptoms of congestive heart failure. In these patients there was a subsequent decrease in venous pressure as failure disappeared, but all values were in the normal range. This illustrates the value of serial determinations of the venous pressure since some patients may have an elevated venous pressure although the actual value is in the normal range. In other patients, venous pressure on admission was high but dropped rapidly into the normal range, after bed rest alone in some cases, although the weight loss and disappearance of the picture of congestive heart failure occurred gradually over the subsequent few days. Therefore, in such patients, a single venous pressure measurement would be misleading.

Most patients displayed concordant changes in weight and venous pressure, both while recovering or decompensating. This suggests a probable relationship between the two. However, in several patients, either the venous pressure or weight began changing prior to the other. This variable behavior of the venous pressure in congestive heart failure must be explained.

Recent studies have shown that the behavior of the tissue pressure in congestive heart failure is also variable.[31-35] The venous pressure and the tissue pressure are directly inter-related since they are hydrostatic forces on either side of the capillary wall which is freely permeable to water and crystalloids. The behavior of the tissue pressure depends, in part, on the anatomic location of the tissues and their distensibility.[36] Therefore, it would seem that the behavior of the venous pressure would depend at least partly on the condition of the tissues as they are subjected to variations in tissue fluid volume. Using the data available in the literature, criteria were drawn up to determine the condition of the tissues in the patients studied. From these (Table IV), the behavior of the venous pressure, that is, the time relation of the initial change in weight to change in venous pressure, was predicted. The predicted behavior agreed with the actual behavior in twenty-seven of the thirty-one cases. Three cases with marked ascites were excluded. These all showed a weight decrease prior to a drop in venous pressure, although when the criteria were applied to these patients it was predicted that their venous pressure and weight should fall concordantly. From this, it seems plausible to assume that the initial weight decrease represented a clearing of the ascites rather than a decrease of edema fluid in the tissues.

The patients who recovered from congestive heart failure with a simultaneous decrease in weight and venous pressure (Group 1) showed initially a faster rate of fall of venous pressure than of weight. This would be expected in view of the relation of the venous pressure to the tissue pressure, as previously discussed. Of the patients showing a simultaneous gain in weight and venous pressure (Group 4), three had recently been in failure. These were expected to show a rise in weight prior to a rise in venous pressure according to the criteria of Table IV. The small graph (Fig. 4) shows that the weight did rise at a faster rate initially than did the venous pressure. The fourth patient had not been in congestive heart failure before. His venous pressure rose at a faster rate than his weight, although this is concealed by the averaging of all four patients (small graph, Fig. 4). These findings are in accord with the hypothesis that the behavior of the venous pressure is affected by the state of the tissues. The relative rates of change in weight and venous pressure in the other four groups may also be explained as a function of the condition of the tissues. The close correlation in these patients of the behavior of the venous pressure with the condition of the tissues is significant. Perhaps the cardiac function has less direct influence on the venous pressure in congestive heart failure than does the state of the tissues. These findings support the work of Starr.[37]

TABLE IV. CRITERIA FOR EVALUATING THE CONDITION OF THE TISSUES AFFECTED BY CARDIAC EDEMA WITH THE PREDICTED BEHAVIOR OF THE VENOUS PRESSURE FOR EACH CONDITION

CRITERIA	TISSUE	PATIENT	PREDICTED BEHAVIOR OF VENOUS PRESSURE
1 No previous edema 2 No recent edema 3 Moderate edema of short duration	Normal	Recovering Decompensating	Decreases with wt.* loss Increases with wt.* gain
1 Recent edema 2 Frequent previous episodes of edema 3 Marked edema of long duration 4 Edema receding	Easily distensible	Recovering Decompensating	Decreases before wt.* loss Increases after wt.* gain
1 Slight edema present in patient decompensating 2 Fibrotic tissue (scleroderma)	More resistant to distention than normal tissue	Recovering Decompensating	Decreases after wt.* loss Increases before wt.* rise

*Weight change as measurable clinically (scales accurate to one-fourth pound).

From this, it would seem that any implications as to the role of the venous pressure in the production of the syndrome of congestive heart failure which are based on observations on patients recovering from congestive heart failure would not be valid, since the condition of the tissues in decompensation and recovery is different.

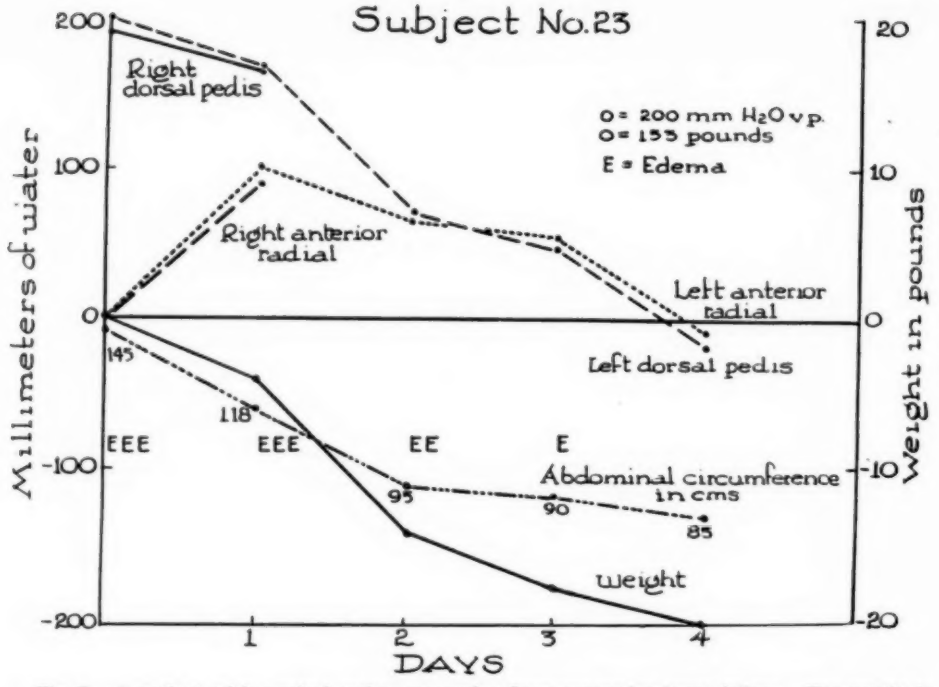

Fig. 7.—A patient with marked ascites recovering from congestive heart failure. The weight decrease preceded both the venous pressure drop and the disappearance of the edema but was concordant with clearing of the ascites. The venous pressures in arms and legs approached each other as the ascites cleared (abdominal circumference).

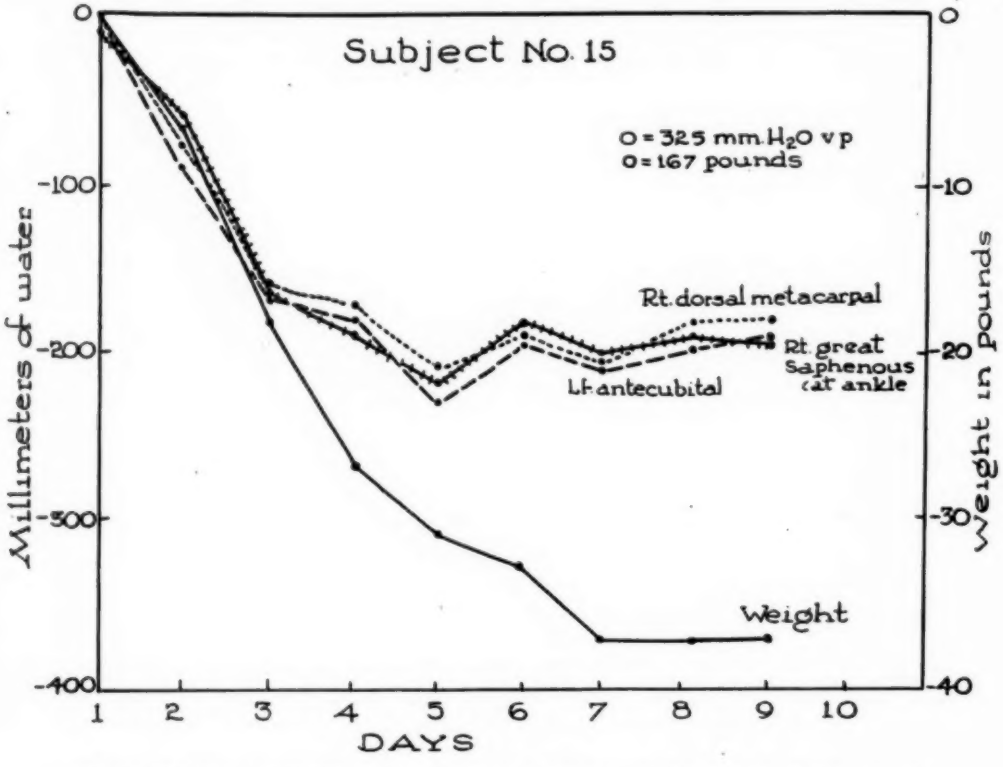

Fig. 8.—The close correlation of venous pressure in the arms and leg of a patient recovering congestive heart failure is shown; average difference, 12 mm. H_2O, with a maximum of 20.

Of the four patients showing a weight loss prior to venous pressure decrease, three had marked ascites. In these patients, initially, the pressure in the veins of the legs was higher than in the veins of the arms, but as the ascites cleared the pressures in all extremities approached each other (Fig. 7). This phenomenon has been reported.[38]

It should be noted that in the absence of ascites simultaneous venous pressures in all extremities varied within a small range (Fig. 8). In general, the wide variation in venous pressure described for the various veins of normal persons[18] was not found in diseased patients with heart disease.

SUMMARY

1. Daily determinations of weight and venous pressure were made during thirty-four significant changes in the stage of chronic congestive heart failure in twenty-three patients. This included twenty-six instances of recovery and eight of decompensation.

2. In general, the venous pressure and the weight varied concordantly. In some patients, either weight or venous pressure began changing prior to the other.

3. The findings indicate that it is not established that an elevation in either weight or venous pressure need precede the other in the development of the syndrome of chronic congestive heart failure, and that depending on the condition of the tissues, either of the two might evidence a clinically detectable rise prior to the other.

4. The behavior of the venous pressure in the patients studied confirms the value of this procedure in the diagnosis and proper clinical evaluation of congestive heart failure, especially when serial determinations are made.

5. The dependence, in part at least, of the venous pressure on the condition of the tissues is demonstrated.

CONCLUSION

In all phases of the syndrome of congestive heart failure, changes in the venous pressure and in the degree of congestion are concordant. Any initial discordance in the time relation of change in venous pressure to change in weight associated with edema can be explained by the state of those tissues affected by edema formation.

ACKNOWLEDGEMENT

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THE INFLUENCE OF SUPRADIAPHRAGMATIC SPLANCHNICECTOMY ON THE HEART IN HYPERTENSION

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SURGICAL treatment has been submitted by Peet and Isberg[1] as a measure capable of arresting and sometimes reversing, in a significant percentage of cases, the progressive deteriorating course of arterial hypertension. This opinion has been founded on the results of a long-term study of a large group of hypertensive patients treated by splanchnic resection. The operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy has been performed in more than 1,500 hypertensive patients at the University Hospital since November, 1933.

The purpose of the present study has been to obtain information concerning the cardiac aspects in arterial hypertension and how these have been influenced by surgical treatment. In order that temporary benefits from the operation be eliminated before judgment was passed, the results in only those cases operated upon five to thirteen years ago have been considered.

Studies of surgically treated hypertensive patients have suggested that the operation has influenced the destiny of the heart in hypertension. It was first recognized in 1934 that significant improvement in abnormal electrocardiograms and definite reduction in heart size occurred in some cases following splanchnicectomy. These clinical phenomena were first reported in 1939 by Braden and Kahn,[2] associates of Peet. In 1940, the results in 350 consecutive, surgically treated cases were evaluated by Peet, Woods, and Braden,[3] and again it was pointed out that cardiac enlargement and abnormal electrocardiograms were sometimes beneficially improved after operation. Others[4,5] have recently confirmed the effect of sympathectomy on the electrocardiogram in hypertension.

Each of the foregoing reports dealt with patients who could be followed only for a relatively short period of time. Electrocardiograms and heart size were reported as improved in cases followed only six months and longer. The present study is concerned entirely with the prolonged effects of splanchnicectomy; all patients have been followed from five to twelve years since operation.

MATERIAL

Between November, 1933, and December, 1941, 720 cases of arterial hypertension were surgically treated. The operative procedure consisted of bilateral resection of the greater, lesser, and least splanchnic nerves, and excision of the eighth, ninth, tenth, eleventh, and twelfth thoracic sympathetic ganglia. In

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the early operations, in addition to the splanchnic nerves, only the lower three dorsal ganglia were removed. The operative mortality was 3.2 per cent. During the eight years, 162 cases of malignant hypertension were operated upon, and when these are excluded, the operative mortality for the series is 1.6 per cent.

Adequate preoperative and postoperative information with respect to cardiac status has been obtained in 384 cases. Both an electrocardiogram and teleroentgenogram were procured in each of the 384 patients prior to operation; physical examinations were performed both in the departments of internal medicine and neurosurgery. Thus, a definite diagnosis concerning whether or not organic heart disease complicated the hypertension could be made in each instance. The cases of malignant hypertension, surgically treated during the same years, are not included in this study; the diagnosis of malignant hypertension was made only in those patients who showed definite papilledema of 1 diopter or more and a recent, rapidly progressive, downhill clinical course. It is felt that malignant hypertension is a distinct disease entity in itself, and a study of this disease will be reported separately.[6]

FINDINGS

Survival Rates.—Of the 384 cases of arterial hypertension in this series, 257 had definite organic heart disease prior to operation, confirmed by an abnormal electrocardiogram or teleroentgenogram showing cardiac enlargement or both. Of these patients with hypertensive heart disease, 60 per cent were alive five to twelve years postoperatively (Table I). Of the 127 hypertensive patients with normal hearts, 93 per cent were alive five to twelve years after operation. The five-to-twelve-year survival rate for the entire series of 384 is 71 per cent.

The fifty-nine persons who had sustained a cerebral accident in addition to having hypertensive heart disease prior to operation have a considerably lower survival rate than those with cardiac involvement and no cerebrovascular complication. Only 46 per cent of the former were living after five to twelve postoperative years, while 64 per cent of the latter were living.

TABLE I. SURVIVAL RATES IN THREE HUNDRED EIGHTY-FOUR CASES OF HYPERTENSION

PREOPERATIVE STATUS	CASES	DEATHS	5-TO-12 YEAR SURVIVALS	
Normal heart	127	9	118 (93%)	
Organic heart disease	198	71	127 (64%)	(60%)
Heart disease plus cerebrovascular disease	59	32	27 (46%)	
Totals	384	112	272 (71%)	

The Electrocardiogram.—An electrocardiogram was considered abnormal only when one or more of the following findings was present: (1) definite left

axis deviation ($R_1 + S_3 = 25$ mm. or more); (2) inversion of T waves in Lead I, in Leads I and II, or in Leads II and III; (3) bundle branch block; and (4) evidences of previous myocardial infarction.

An abnormal electrocardiogram was considered "significantly improved" five years and more after operation only when: (1) inverted T waves returned to an upright configuration with an amplitude of 1 mm. or more, or (2) 30° change of electrical axis toward normal occurred with reduction of 8 mm. or more in the value of $R_1 + S_3$. An electrocardiogram with both abnormal T waves and left axis deviation was considered "improved" when either one of these criteria was fulfilled.

A postoperative electrocardiogram was considered to be "worse" when any one of the following appeared: (1) 1 mm. or more depression of a previously upright or flat T wave in Lead I or II; (2) a 30° change of electrical axis toward abnormal, with increase of 8 mm. or more in the value of $R_1 + S_3$; (3) evidences of myocardial infarction; and (4) bundle branch block.

Two hundred nineteen patients had abnormal preoperative electrocardiograms; 60 per cent of these persons were still living five to twelve years postoperatively. Of the 165 hypertensive patients with normal electrocardiograms, 85.5 per cent were alive five years and more after operation.

Table II enumerates the incidence of the various electrocardiographic abnormalities in this series, the subsequent deaths with each abnormality, and the electrocardiographic status of the living patients five years and more after operation. It is seen that patients with inverted T waves in both Leads I and II have the highest death rate; but when these patients survive five years and more their tracings are likely to be "significantly improved."

One hundred eighty-four living patients had recent electrocardiograms taken, five to twelve years after operation (Table III). Of the eighty-three who had abnormal tracings prior to operation, 41 per cent now show "significant improvement," 55.4 per cent show no change, and 3.6 per cent have progressed to worse changes. All patients who had sustained a coronary occlusion or were ever given digitalis were automatically excluded from the "significantly improved" classification.

Of the 101 patients whose electrocardiograms were normal preoperatively, 94 per cent have maintained an unchanged, normal tracing during the long postoperative period; in 6 per cent the tracing have become abnormal. Six series of electrocardiograms are shown in Figs. 1, 2, 3, 4, 5, and 6. All were abnormal before operation and improved notably after operation.

There is a definite correlation between postoperative improvement in the electrocardiogram and postoperative reduction in blood pressure. Of the thirty-four patients who had an abnormal preoperative electrocardiogram and who have maintained a "significantly improved" tracing for five years and more after operation, six have maintained normal blood pressure levels (140/90 or less),

and twenty-six have maintained a significant reduction of 15 mm. or more diastolic pressure during the postoperative period. Only two patients with improved electrocardiograms showed no improvement in diastolic pressure (Table IV).

TABLE II. THE ELECTROCARDIOGRAM IN THREE HUNDRED EIGHTY-FOUR HYPERTENSIVE PATIENTS

PREOPERATIVE STATUS	CASES	DEATHS	PATIENTS ALIVE FIVE TO TWELVE YEARS POSTOPERATIVELY				
			CASES LIVING	SIGNIFICANT IMPROVEMENT IN ECG	NO SIGNIFICANT CHANGE	WORSE	NO FOLLOW-UP ECG
Normal ECG	165	24	141	—	95	6	40
Abnormal ECG	219	88	131	34	46	3	48
Inverted T_1	18	6	12	4	3	0	5
Inverted T_1 and T_2	54	27	27	13	4	0	10
Inverted T_2 and T_3	14	3	11	2	3	1	5
Definite L.A.D.	42	10	32	2	18	2	10
Both inverted T waves and definite L.A.D.	75	37	38	13	9	0	16
Bundle branch block	5	2	3	0	3	0	0
Evidences of previous myocardial infarction	11	3	8	0	6	0	2

TABLE III. THE INFLUENCE OF SURGICAL TREATMENT ON THE ELECTROCARDIOGRAMS OF ONE HUNDRED EIGHTY-FOUR PATIENTS FIVE TO TWELVE YEARS AFTER OPERATION

PREOPERATIVE STATUS	CASES	POSTOPERATIVE STATUS		
		SIGNIFICANTLY IMPROVED	NO SIGNIFICANT CHANGE	WORSE
Normal ECG	101	—	95 (94%)	6 (6%)
Abnormal ECG	83	34 (41%)	46 (55.4%)	3 (3.6%)

None of the electrocardiographic abnormalities which occurred in this series can be considered a contraindication to surgical treatment. The death rate in the presence of any one of the abnormalities is not so great as to render

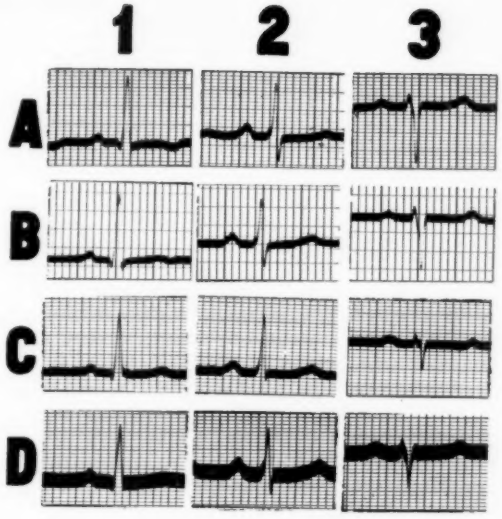


Fig. 1.—Case 1. *A*, (April 11, 1939) preoperative ECG; left axis deviation and inverted T waves in Lead I. Splanchnicectomy was performed on April 15, 1939. *B*, (Oct. 18, 1939) six months postoperative; T waves in Lead I are now upright. *C*, May 9, 1940. *D*, (April 13, 1944) five years postoperative; upright T waves maintained in Lead I, and left axis deviation is less marked than in preoperative tracing.

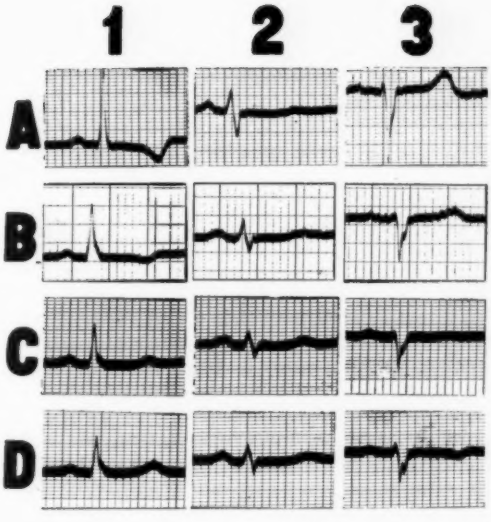


Fig. 2.—Case 2. *A*, (Oct. 18, 1940) preoperative ECG; definite left axis deviation, inverted T waves in Lead I, and flat T waves in Lead II. Splanchnicectomy was performed on Oct. 24, 1940. *B*, (April 3, 1941) six months postoperative; T waves in Lead I are less deeply inverted than previously. *C*, (Sept. 1, 1944) four years postoperative; shows almost complete retrogression of the 1940 ECG changes; T waves are now normal and the slight axis deviation is within normal limits. *D*, (Sept. 27, 1945) five years postoperative; ECG remains within normal limits.

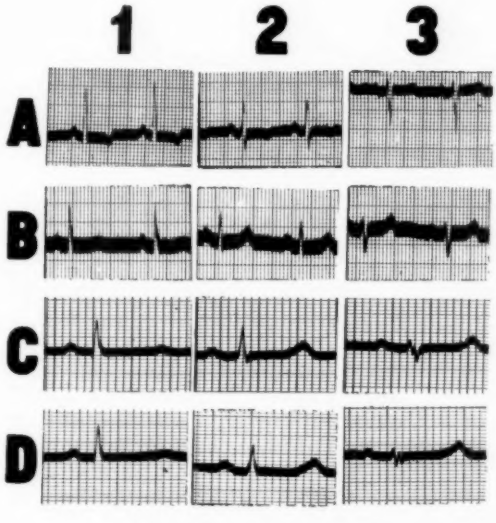


Fig. 3.—Case 3. *A*, (Nov. 22, 1934) preoperative ECG; definite left axis deviation and inverted T waves in Lead I. Splanchnicectomy was performed on Dec. 3, 1934. *B*, (Sept. 28, 1937) three years postoperative; slight left axis deviation and upright T waves in Lead I. *C*, Aug. 25, 1938. *D*, (Aug. 27, 1940) six years postoperative; normal ECG. The Q-T interval of the last two tracings is not abnormally long when compared to the heart rate which was 58 per minute.

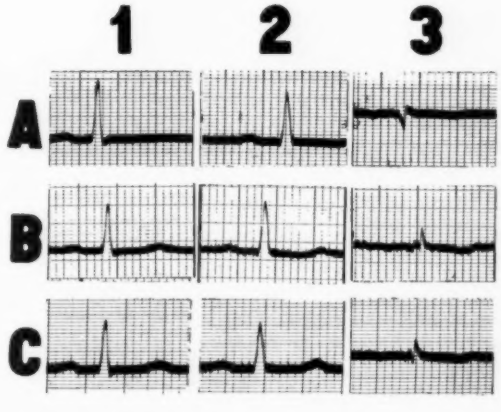


Fig. 4.—Case 4. *A*, (April 2, 1940) preoperative ECG; flat T waves in Lead I and slight inversion of T waves in Leads II and III. Splanchnicectomy was performed on April 11, 1940. *B*, (Nov. 6, 1940) six months postoperative; slight inversion of T waves in Leads II and III. *C*, (July 26, 1945) five years postoperative; normal ECG.

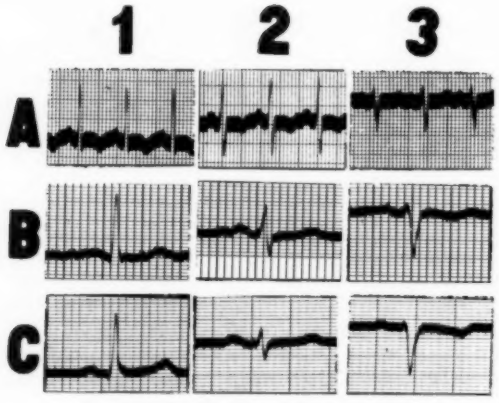


Fig. 5.—Case 5. *A*, (March 1, 1937) preoperative ECG; left axis deviation and inverted T waves in Leads I and II. Splanchnicectomy was performed on March 6, 1937. *B*, (Sept. 8, 1938) eighteen months postoperative; T waves are now normal. *C*, (Aug. 7, 1946) normal T waves have been maintained for nine years since operation.

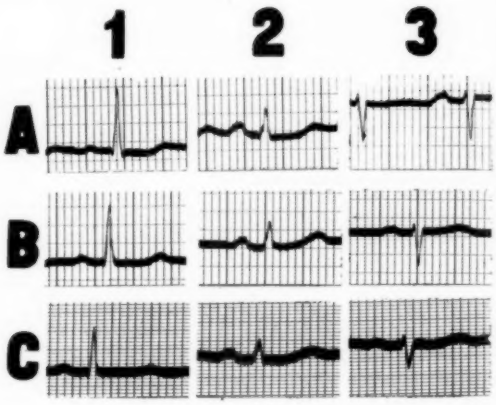


Fig. 6.—Case 6. *A*, (Aug. 4, 1938) preoperative ECG; definite left axis deviation with depressed RS-T segments and inverted T waves in Leads I and II. Splanchnicectomy was performed on Aug. 18, 1938. *B*, (April 11, 1939) eight months postoperative; T waves are now upright in Leads I and II. *C*, (Aug. 9, 1946) eight years postoperative; ECG is within normal limits; T waves are upright and axis deviation is no longer outside normal limits.

splanchnic resection futile, and each of the abnormalities, except bundle branch block and previous myocardial infarction, potentially may be significantly improved following operation.

Heart Size.—Heart size in this series has been followed by serial teleroentgenograms taken before and after splanchnic resection. The prediction tables of Hodges, P. C., and Eyster[7] for frontal area, and the prediction tables of Hodges, F. J., and Eyster[8] for transverse diameter have been used. Table V lists the criteria for determining relative extent of cardiac enlargement on the basis of the per cent variation from predicted normal.

TABLE IV. CORRELATION OF POSTOPERATIVE ECG CHANGE WITH POSTOPERATIVE BLOOD PRESSURE CHANGE IN EIGHTY-THREE PATIENTS WHO HAD ABNORMAL ECG PREOPERATIVELY

POSTOPERATIVE ECG	CASES	POSTOPERATIVE BLOOD PRESSURE		
		REDUCED TO NORMAL	15 MM. OR MORE REDUCTION IN DIASTOLIC PRESSURE	NO CHANGE OR WORSE
Significant improvement	34	6	26	2
No significant change	46	2	28	16
Worse	3	0	0	3

In order for a postoperative teleroentgenogram to be considered as demonstrating "significant decrease" in heart size from the preoperative state, there must have occurred a 10 per cent or more decrease in frontal area or transverse diameter variation and change to the next category toward normal, according to Table V. The criterion for "significant increase" is that a 10 per cent or more increase in frontal area or transverse diameter variation has occurred.

TABLE V. CRITERIA FOR DETERMINING EXTENT OF CARDIAC ENLARGEMENT

HEART SIZE	VARIATION FROM PREDICTED NORMAL	
	CARDIAC AREA	TRANSVERSE DIAMETER
Upper limit of normal	+ 10%	+ 10%
Slight cardiac enlargement	11% to 20%	11% to 20%
Moderate cardiac enlargement	21% to 50%	21% to 50%
Marked cardiac enlargement	Greater than 50%	Greater than 50%

Cardiac enlargement was present in 177 cases, or 43 per cent of the series. Of the hypertensive subjects in whom an enlarged heart was demonstrated, 50 per cent did not survive five to twelve years after the operation. It is seen that in hypertensive heart disease, patients with cardiac enlargement have a somewhat poorer prognosis than those with an abnormal electrocardiogram. Of those with normal sized hearts, 88.4 per cent were living (Table VI).

TABLE VI. HEART SIZE IN THREE HUNDRED EIGHTY-FOUR HYPERTENSIVE PATIENTS

PREOPERATIVE STATUS	CASES	DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY				
			CASES LIVING	SIGNIFICANT DECREASE IN HEART SIZE	NO CHANGE	INCREASE IN HEART SIZE	NO FOLLOW-UP TELEROENT-GENOGRAM
Normal heart size	207	24	183	—	123	10	50
Cardiac enlargement	177	88	89	25	26	6	32
Slight cardiac enlargement	83	33	50	11	16	5	18
Moderate cardiac enlargement	76	38	38	14	10	1	13
Marked cardiac enlargement	18	17	1	—	—	—	1

Teleroentgenograms were recently obtained in 190 living patients five to twelve years after operation. Of the fifty-seven patients with preoperative cardiac enlargement, significant decrease in heart size was demonstrated in 44 per cent, 45.6 per cent showed no change, and in 10.4 per cent, further increase in size had occurred (Table VII). Serial teleroentgenograms of four patients whose heart size decreased significantly after operation are shown in Figs. 7, 8, 9, and 10.

TABLE VII. THE INFLUENCE OF SURGICAL TREATMENT ON HEART SIZE, MEASURED ON TELEROENTGENOGRAMS OF ONE HUNDRED NINETY PATIENTS FIVE TO TWELVE YEARS AFTER OPERATION

PREOPERATIVE STATUS	CASES	POSTOPERATIVE STATUS		
		SIGNIFICANT DECREASE IN HEART SIZE	NO CHANGE	SIGNIFICANT INCREASE IN HEART SIZE
Normal heart size	133	——	123 (92.5%)	10 (7.5%)
Cardiac enlargement	57	25 (44%)	26 (45.6%)	6 (10.4%)

Of the 133 patients with normal heart size prior to operation, 92.5 per cent maintained an unchanged normal status for five years and more. Cardiac enlargement occurred during the long postoperative period in 7.5 per cent of those who had hearts of normal size before splanchnic resection.

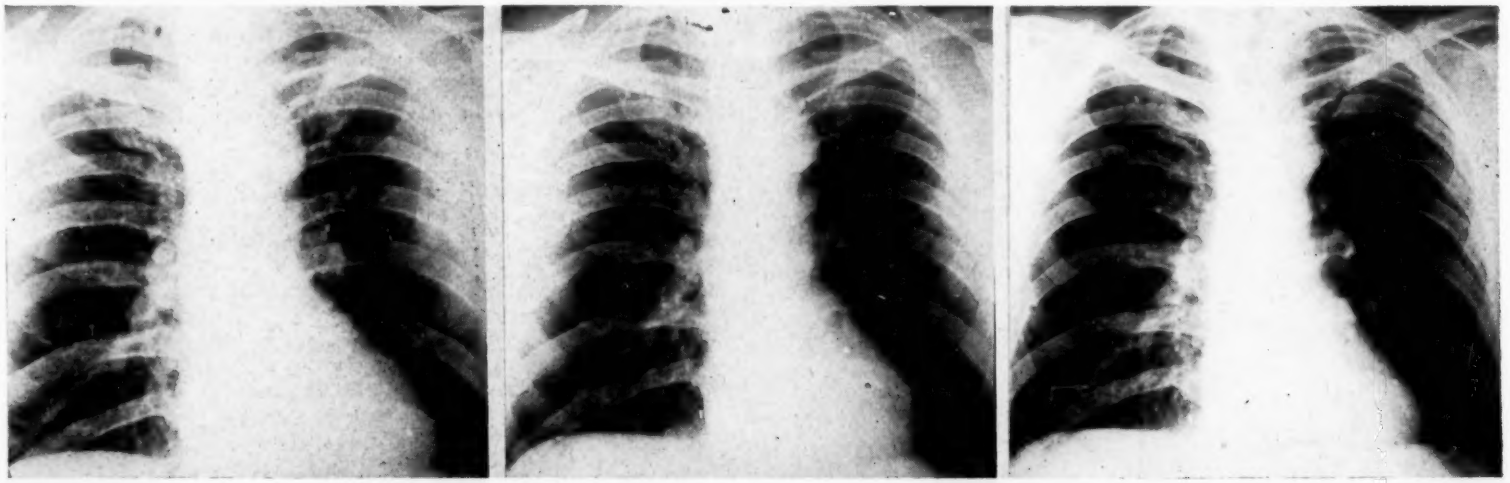
It appears that reduction in blood pressure is necessary in order for a significant decrease in heart size to occur. In all twenty-six persons in whom definite decrease in heart size was demonstrated, blood pressure levels have either been reduced to within normal range, or a significant reduction of 15 mm. or more in diastolic pressure has been maintained (Table VIII).

TABLE VIII. CORRELATION OF POSTOPERATIVE HEART SIZE CHANGE WITH POSTOPERATIVE BLOOD PRESSURE CHANGE IN FIFTY-SEVEN PATIENTS WHO HAD PREOPERATIVE CARDIAC ENLARGEMENT

POSTOPERATIVE HEART SIZE	CASES	POSTOPERATIVE BLOOD PRESSURE		
		REDUCED TO NORMAL	15 MM. OR MORE REDUCTION IN DIASTOLIC PRESSURE	NO CHANGE OR WORSE
Significant decrease in size	25	5	20	0
No change	26	1	15	10
Increase in heart size	6	0	1	5

4/17/36.	Variation		10/5/37.	Area	T. D.	9/6/45	Area	T. D.
	Area	T. D.		−1%	−1%		+4%	+2%
	+50%	+12%						

Fig. 7.—Case 7. Decrease in size of heart after operation, splanchnicectomy performed on April 24, 1936. The heart size is expressed in percentage of the predicted area as transverse diameter.

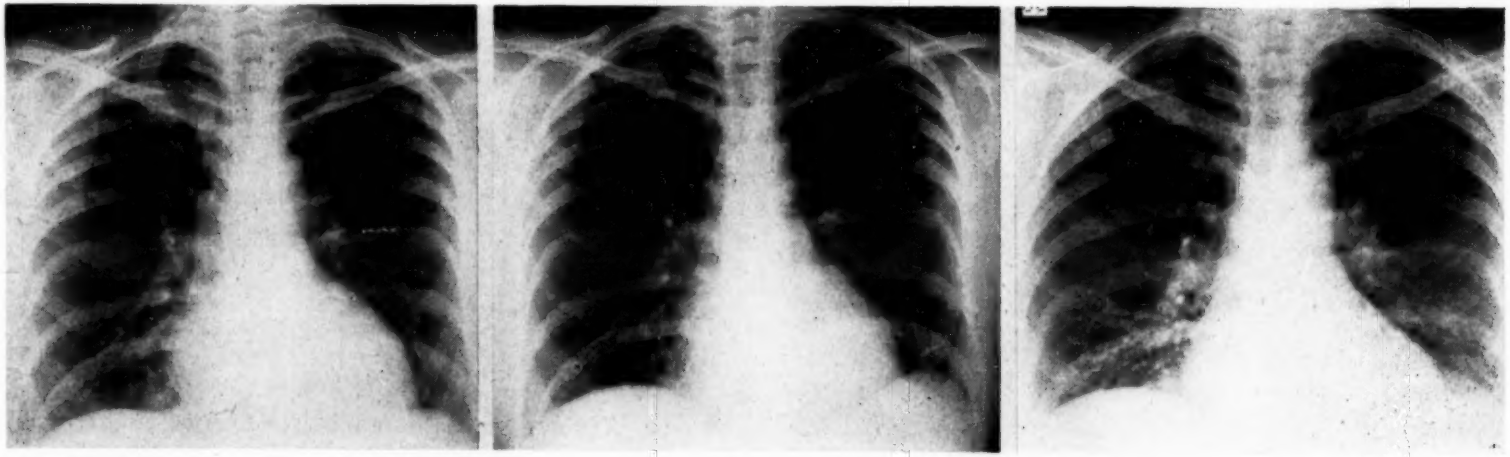


4/11/39.	Variation		10/18/39.	Area	T. D.	1/13/44.	Area	T. D.
	Area	T. D.		−6%	−5%		−8%	−7%
	+13%	+8%						

Fig. 8.—Case 8. Splanchnicectomy performed on April 15, 1939.

1/17/38.	Variation		9/23/38.	Area	T. D.	5/28/45.	Area	T. D.
	Area	T. D.		−3%	−6%		+6%	−19%
	+16%	+11%						

Fig. 9—Case 9. Splanchnicectomy performed on Feb. 4, 1938.



3/17/38.	Variation		4/12/39.	Area	T. D.	8/23/45.	Area	T. D.
	Area	T. D.		+4%	+6%		−2%	+8%
	+23%	+20%						

Fig. 10—Case 10. Splanchnicectomy performed on March 28, 1938.

Splanchnic resection has nothing to offer the hypertensive patient with *marked* cardiac enlargement. When the variation above the predicted normal is greater than 50 per cent for area or transverse diameter, the outlook is grave, and it cannot be influenced by splanchnicectomy. Of the eighteen patients who had marked cardiac enlargement, only one has survived five years.

Cardiac Symptoms.—One or more of the cardiac symptoms of exertional dyspnea, paroxysmal nocturnal dyspnea, palpitation, swollen ankles, and anginal seizures were present in 54 per cent of the series. Eighty-five per cent of the patients complaining of cardiac symptoms had definite organic heart disease, confirmed by an abnormal electrocardiogram, by a teleroentgenogram showing cardiac enlargement, or by both.

Of 162 patients who complained of exertional dyspnea, 100 had definitely enlarged hearts. Of the patients with exertional dyspnea, 38.3 per cent did not have cardiac enlargement (Table IX).

Fifty-nine per cent of the patients with cardiac complaints have survived five to twelve postoperative years. Of the 124 persons who had preoperative symptoms and who were still living, 60 per cent were improved, 37 per cent have obtained no relief, and 3 per cent were worse.

The patient with paroxysmal nocturnal dyspnea has very little to gain from surgical treatment of his hypertension. There were twenty-four cases with this complaint, and only three survived five years or more. Each of the twenty-four cases had an abnormal electrocardiogram and all but one also had cardiac enlargement.

Sixty-eight patients complained of characteristic anginal seizures, and 84 per cent of these had organic heart disease, confirmed by abnormal electrocardiogram or cardiac enlargement by teleroentgenogram or both. Sixty-two per cent of the patients with angina survived five to twelve years, and more than one-half of those still living have obtained definite relief from the seizures. Fourteen patients have been completely relieved of angina for five years or more since splanchnic resection.

Of the 174 hypertensives who had no cardiac complaints, 85 per cent are still living. Ninety-three per cent still have no cardiac symptoms, while 7 per cent have developed symptoms during the long postoperative period.

Physical Signs.—Abnormal cardiac physical signs were present in 160 patients, or 24 per cent of the series, and 84 per cent of these had confirmed organic heart disease (Table X).

Fifty-eight per cent of patients with a systolic murmur and 60.6 per cent of patients with an accentuated aortic second sound were living five to twelve years after operation. This approximates the overall 60 per cent survival rate of the group with hypertensive heart disease.

Only 23.3 per cent of the patients with gallop rhythm and 33.2 per cent of those with an accentuated pulmonic second sound have lived five to twelve years

TABLE IX. CARDIAC SYMPTOMS

PREOPERATIVE STATUS	CASES	CONFIRMED HEART DISEASE				DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY			
		CASES	BOTH ABNORMAL ECG AND CARDIAC ENLARGEMENT	ABNORMAL ECG ONLY	CARDIAC ENLARGEMENT ONLY		CASES	IMPROVED	SAME	WORSE
No cardiac symptoms	174	78	30	32	16	26	148	—	138	10
Symptoms present	210	179	109	48	22	86	124	74	46	4
Exertional dyspnea	162	137	85	37	15	74	88	48	37	3
Paroxysmal nocturnal dyspnea	24	24	23	1	0	21	3	2	1	0
Palpitation	50	39	22	13	4	18	32	21	11	0
Swollen ankles	30	27	21	5	1	16	14	8	6	0
Angina	68	57	37	16	4	26	42	23	18	1

TABLE X. PHYSICAL SIGNS

PREOPERATIVE STATUS	CASES	CONFIRMED HEART DISEASE				DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY			
		CASES	BOTH ABNORMAL ECG AND CARDIAC ENLARGEMENT	ABNORMAL ECG ONLY	CARDIAC ENLARGEMENT ONLY		CASES	IMPROVED	SAME	WORSE
No physical signs	224	123	50	49	24	45	179	—	170	9
Physical signs present	160	134	89	31	14	67	93	13	78	2
Systolic murmur	86	70	45	15	10	36	50	6	44	
Accentuated A_2	61	50	33	8	9	24	37	5	32	
Accentuated P_2	6	6	3	1	2	4	2	0	2	
Gallop	30	30	25	5	0	23	7	5	2	

following operation. Although splanchnic resection offers only a slim chance for prolonged survival to these patients, the presence of either one of these two signs does not contraindicate operation.

Congestive Heart Failure.—Sixteen patients in congestive heart failure were digitalized prior to splanchnicectomy. Only five of these patients were living after five years or more. One patient died on the day following operation.

The hypertensive cardiac patient who requires digitalization has a grave outlook. But since such a patient stands one chance in three for prolonged survival following splanchnic resection, he should not be denied the operation once he is properly digitalized.

Coronary Occlusion.—Eleven patients who had had a coronary occlusion with myocardial infarction were subsequently treated by splanchnicectomy for their hypertensive disease. Eight of these persons were still living five to nine years after operation. The three deaths each resulted from a subsequent coronary occlusion, one to four years after operation.

This prolonged survival of 72.7 per cent of the hypertensive patients who had also had a coronary occlusion should lead one to consider seriously splanchnicectomy in hypertensive patients six to twelve months following a coronary occlusion.

Coronary occlusion has occurred in twenty-four patients out of the entire series from three months to eleven months after operation. Six have survived myocardial infarction, and were still living five to ten years after splanchnic resection. It has been the cause of death in eighteen cases; 17 per cent of th 112 deaths in this series have resulted from coronary occlusion. Goldring and Chasis[9] have compiled the causes of death in patients with hypertensive disease as reported by various authors, and coronary thrombosis accounted for 13.6 per cent of the total deaths in six different series.

Of the twenty-four cases who sustained a coronary occlusion subsequent to splanchnicectomy, twenty had both an abnormal electrocardiogram and cardiac enlargement before operation. Five had anginal seizures preoperatively, and in four patients gallop rhythm was present prior to splanchnic resection.

DISCUSSION

The study of cardiac aspects in 384 cases of arterial hypertension treated by splanchnic resection five to thirteen years ago have revealed the following:

1. Sixty per cent of patients with hypertensive heart disease were still living five to twelve years after splanchnicectomy.

2. Ninety-three per cent of hypertensive patients with normal hearts were still living five to twelve years after operation.

3. Patients whose electrocardiograms show inverted T waves in both Leads I and II, or both definite left axis deviation and abnormal T waves, have a 50 per cent chance for prolonged survival following splanchnicectomy.

4. Of the patients still alive, 41 per cent of those with abnormal preoperative electrocardiograms recently showed significant improvement in their tracings five years or more after operation, and 44 per cent of those with preoperative cardiac enlargement recently showed significant decrease in heart size.

5. Practically all patients who have shown improvement in electrocardiogram or decrease in heart size have maintained a significant reduction in blood pressure.

6. Fifty per cent of hypertensive patients in whom an enlarged heart was demonstrated have not survived five to twelve years.

7. Splanchnic resection is of no avail in cases of marked cardiac enlargement with a variation greater than 50 per cent of predicted normal for frontal area or transverse diameter.

8. The patient with paroxysmal nocturnal dyspnea has little chance for. benefit from splanchnic resection; only 12.5 per cent survived five years or more.

9. Anginal seizures were frequently relieved following splanchnicectomy.

10. Of patients with gallop rhythm prior to operation, 23.3 per cent have survived five years or more.

11. The hypertensive patient in congestive heart failure which requires digitalization preparatory to splanchnicectomy stands one chance in three for prolonged survival following operation.

12. Eight out of eleven hypertensive patients who had had a coronary occlusion and were subsequently treated with splanchnic resection were still living five to nine years after operation.

Canabal and associates[10] have recently supplied valuable information concerning the spontaneous evolution of the electrocardiogram in hypertension. They reported on a control series of fifty cases of hypertension with electrocardiograms taken over a period of five years or more. They found that in 10 per cent of the cases there was questionable-to-slight improvement of the electrocardiogram; that in 40 per cent, the tracings remained unchanged; and that in 50 per cent, they became worse. The spontaneous trend of the electrocardiogram in hypertension is to become worse as time goes on.

When one compares this control group with the eighty-three hypertensive patients who had abnormal electrocardiograms prior to splanchnic resection, and of whom 41 per cent showed significant improvement in their tracings five to twelve years later, and of whom only 3.6 per cent developed more serious electrocardiographic changes, then one may justifiably state that splanchnicectomy has beneficially influenced the destiny of the hypertensive patients with abnormal electrocardiograms who have been fortunate enough to have lived five years and longer after operation.

There were 127 hypertensive patients who showed no evidences of cardiac disease at the time of operation. Nine subsequently died, and eight, who were still living, have developed heart disease, confirmed by an abnormal electrocardiogram or cardiac enlargement by teleroentgenogram or by both. Of the

hypertensive patients with normal hearts prior to operation, 86.6 per cent were living and had maintained a normal cardiac status for five to twelve years; 6.4 per cent were still living but had progressed to heart disease; and 7 per cent were dead. Has splanchnic resection significantly arrested progression to heart disease in hypertensive patients with normal hearts? Although the preceding figures appear appealingly good, no definite statement can as yet be made, for no appropriate control group is available for comparison.

Has splanchnic resection prolonged the lives of patients with hypertensive heart disease? Again no definite statement can be made even though the statistics of this series evoke a sympathetic response. The literature is inadequate concerning the life history of hypertensive patients with organic heart disease, and no fair comparisons can be made.

There are several reports in the literature on survival in hypertension, but in none are the hypertensive patients with heart disease separated from those with normal hearts. In Janeway's[11] series of 458 hypertensive patients, one-half of the men died within four years and one-half of the women within five years; by the tenth year, one-half of the remainder had died. Hamman[12] had a 78 per cent mortality at the end of ten years. King and associates[13] followed 481 patients for ten to sixteen years, and the mortality was 73 per cent. In one-half of their cases, the discovery of hypertension was purely an incidental finding.

Wagener and Keith[14] have presented a five-to-nine-year follow-up study of 219 cases of arterial hypertension, and they have offered the series as a control for any specific form of therapy. Their cases are classified according to retinal changes; the incidence of heart disease in this series is not known. One hundred forty-six of their patients had malignant hypertension. The remaining seventy-three patients form a series comparable to the 384 patients presented in this paper. Of their hypertensive patients without papilledema, 24.6 per cent have survived five to nine years since the initial examination. Of the 384 hypertensives without papilledema in our series, 71 per cent have survived five to twelve years since operation. It appears that splanchnic resection may have beneficially influenced survival in hypertensive patients.

SUMMARY

This is a study of the cardiac aspects in 384 patients with arterial hypertension, treated surgically by the operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. The findings suggest that this surgical treatment may have beneficially influenced the destiny of a significant percentage of hypertensive patients.

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THE ELECTROCARDIOGRAM OF MAN IN SEMISTARVATION AND SUBSEQUENT REHABILITATION

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FROM the current textbooks and monographs on cardiology it seems to be believed that inanition has no significant effects on the heart and its function. Elsewhere, however, we have shown that there are, in fact, profound changes in the size and function of the heart in semistarvation and subsequent rehabilitation.[1] The present paper is an analysis of the associated electrocardiographic findings. While this material has primary reference to famine conditions, it should be noted that similar physiologic states occur in all wasting diseases; indeed, the majority of chronic illnesses tend to produce changes in this direction.

The literature on electrocardiographic changes in chronic semistarvation and prolonged undernutrition is very small. Benedict and co-workers[2] reported that the electrocardiograms in their experiments on undernutrition were within "normal" limits, but no quantitative analysis was made. The degree of semistarvation attained in Benedict's series was mild compared to that in the series to be reported here and to the conditions in famine areas. The remaining scanty data in the literature were obtained from the uncontrolled conditions of war and associated famine; electrocardiograms from the prestarvation state were not available.

Electrocardiographic material was obtained by Tur[3] during the siege of Leningrad in 1941 and 1942. In forty severely undernourished patients, the majority showed sinus bradycardia, right axis shift, and low QRS voltage. In deteriorating patients, there was a progressive tendency to lower T-wave amplitude in the standard leads. In a later group of twenty-four patients, who had presumably suffered more prolonged but less acute inanition, the majority showed subnormal T-wave amplitudes and these were thought to have prognostic significance.

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Cardozo and Eggink[4] found low voltage and sinus bradycardia in twenty-nine cases of severe undernutrition. In addition, the Q-T interval was prolonged, both absolutely and in relation to the cycle rate.

Ellis[5] made electrocardiographic studies on four repatriated prisoners of war, immediately after liberation and during three weeks of rehabilitation; these men were in an advanced state of semistarvation. The most prominent feature was a tremendous prolongation of the Q-T interval. In three cases, the P wave was superimposed on the descending limb of a rounded T wave, and in two cases the S-T segment was depressed. Several other features are discernible in the electrocardiograms reproduced by Ellis. All four patients had a right axis shift and the T waves were small or became small during refeeding. The QRS amplitude decreased during treatment in three patients and was rather low at all times in the fourth patient. In the most cachectic patient a pulsus trigeminus, due to premature ventricular beats, disappeared with refeeding.

The material presented here was obtained from thirty-two young men, previously normal, who underwent twenty-four weeks of semistarvation (after a control period of twelve weeks), and during thirty-two subsequent weeks of rehabilitation. During the semistarvation period, the men lost from 27 to 65 pounds, representing an average of 24 per cent of their original weight. Further details are given elsewhere.[1,6-8] The clinical picture closely simulated that seen in many liberated areas in Europe in the spring of 1945.

METHOD

General Procedure and Experimental Arrangement.—Thirty-two normal young men (age range from 20 to 33 years) resided in the laboratory on a controlled regimen of diet and activity. During a control period (C)* of three months, they were kept at a maintenance diet averaging 3,490 calories. For 167 subsequent days they subsisted on a European type of famine diet, averaging daily 1,660 calories, including 30 Gm. of fat, 54 Gm. of protein, 1.29 mg. of thiamine, 0.71 mg. of riboflavin, and 20.7 mg. of niacin.

At the end of the semistarvation period, the thirty-two subjects were subdivided into four groups for the first twelve weeks (to R12) of rehabilitation (Groups Z, L, G, and T), who received diets differing in steps of 400 calories daily; Group Z averaged 2,500 calories daily in this period. After R12, there were no diet restrictions.

Although electrocardiograms were taken more frequently, we have restricted the detailed analysis to the following periods, which characterize the general trend of the changes during semistarvation: control (C), twelfth and twenty-fourth weeks of semistarvation (S12 and S24), and the twelfth week of rehabilita-

*Throughout the paper, the following legend will be used:
C = control period.
S12 = twelfth week of starvation.
R12 = twelfth week of rehabilitation.

tion (R12). The average body weights of the thirty-two men were 70.0, 56.9, 53.2, and 59.4 kg. at these several times, respectively. Twenty of these men were re-examined after thirty-two weeks of rehabilitation (R32); at that time their body weights, in most cases, exceeded their original control weights.

Electrocardiographic Procedure.—The three standard leads were taken, together with heart sound records, during arrested respiration. An external voltage calibration was used before and after each series, in addition to that incorporated in the instrument (Sanborn). The speed was similarly checked independently. The duration of mechanical systole was calculated as the interval between the start of the major oscillations of the first heart sound and the beginning of the second heart sound. Both Q-T interval and mechanical systole were averaged from five beats, usually in Lead II. The constant K was calculated both for Q-T ($K_{Q\text{-}T}$) and mechanical systole duration (K_{SYST}), using the formula $K = \frac{\text{Q-T (or systole)}}{\sqrt{\text{R-R}}}$. The average heart rate was calculated from ten beats; in addition, the shortest and longest R-R intervals of the whole record were measured. Their difference, absolute and in percentage of the average heart rate, was used as a criterion of arrhythmia. The amplitudes of the P wave, the QRS complex, and the T wave were measured in all leads. The QRS axis and the T axis were calculated, using Dieuaide's procedure. For estimation of the overall magnitude of the QRS complex and the T wave, the sum of the amplitudes in Leads I, II, and III was calculated. The symbols Σ_{QRS} and Σ_T are used to express these values.

After Lead II was taken with arrested respiration, the effect of maximum inspiration was recorded in the same lead. Early and late effects, especially on intervals, were analysed. The statistical significance of the changes in semi-starvation and rehabilitation was calculated by means of the T-test.[9,10]

RESULTS

Interval Changes.—Tables I and II show the average interval changes (heart rate, Q-T interval, systole duration, $K_{Q\text{-}T}$ and K_{SYST}) during starvation and thirty-two weeks of rehabilitation. The P-R interval, QRS interval, and duration of the P wave did not change significantly during starvation and rehabilitation and are, therefore, not included in the tables.

Table I shows the absolute values and standard deviations for the total group of thirty-two subjects for the periods C, S12, S24, and R12 and for twenty subjects for the periods C, S24, R12, and R32. Table II shows the differences between the various periods, calculated from Table I. The values of both groups coincide very closely for the periods C, S24, and R12, so that probably the changes at R32 of the group of twenty subjects are representative for the total group of thirty-two subjects.

The slow average heart rate (55.2 beats per minute) during the control period agrees well with many observations on healthy young men made in this

TABLE I. HEART RATE, Q-T INTERVAL, AND SYSTOLE DURATION IN SEMISTARVATION AND REHABILITATION. MEAN VALUES AND STANDARD DEVIATIONS OF THIRTY-TWO AND TWENTY SUBJECTS

FUNCTION	NO. OF SUBJECTS	CONTROL		S12		S24		R12		R32	
		M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$
Heart rate (beats/min.)	32	55.20	6.49	35.3	4.96	37.3	5.15	49.2	6.56	—	—
	20	54.9	—	—	—	37.5	—	50.0	—	58.7	5.03
Range of heart rate absolute	32	9.50	4.16	3.1	1.16	3.4	1.27	7.6	4.50	—	—
	20	9.8	—	—	—	3.3	—	7.2	—	10.4	2.66
Range in per cent of average heart rate	32	14.7	—	8.1	—	8.8	—	14.1	—	—	—
	20	15.3	—	—	—	8.8	—	13.8	—	17.8	4.07
Absolute Q-T (sec. x 100)	32	35.8	2.69	46.1	8.63	45.1	2.55	41.3	2.27	—	—
	20	36.1	—	—	—	45.8	—	41.4	—	39.8	2.71
Absol. mechan. systole duration (sec. x 100)	32	32.5	2.46	39.3	2.39	39.3	2.41	37.2	2.02	—	—
	20	—	—	—	—	—	—	—	—	—	—
$K_{Q\text{-}T}$ (x 100) ($Q\text{-}T/R\text{-}R^{-2}$)	32	37.01	1.8	36.54	1.6	36.34	2.4	38.18	1.7		
	20	37.03	—	—	—	36.43	—	37.94	—	38.69	2.2
K_{SYST} (x 100)	32	33.55	1.6	31.09	1.3	31.55	1.6	34.35	1.5	—	—

laboratory during recent years. The heart rate slowed to 37.3 beats at the end of the semistarvation; it increased again during rehabilitation, but was still below the control value at the twelfth week of rehabilitation. However, a further increase occurred from R12 to R32, and this change was statistically highly significant. The pulse rate at R32 even exceeded the initial rate (C), and this difference was statistically highly significant.

The decrease of the heart rate was associated with a narrowing of the range of the heart rate (variability within the electrocardiogram). This is true for the absolute range as well as for the variability in percentage of the average heart rate. The heart beat is more regular in the starved subject than it is in a normal subject. A pronounced sinus arrhythmia which was present in a few subjects in the control period disappeared completely during semistarvation. In the rehabilitation period the range increased with the heart rate again and sinus arrhythmia returned in those subjects who had sinus arrhythmia before starvation. Expressed as percentage (Table II), the decrease of the range (variability) of the heart rate in starvation (and the increase in rehabilitation) exceeded the decrease of the heart rate.

The absolute Q-T interval and mechanical systole duration increased during semistarvation, as should be expected from the lengthening of the cycle. As shown by the changes of $K_{Q\text{-}T}$ and K_{SYST} during starvation and rehabilitation, the changes in the Q-T interval and in the mechanical systole duration lagged

TABLE II. DIFFERENCES OF INTERVALS, ABSOLUTE AND IN PERCENTAGE OF THE PRECEDING REFERENCE PERIOD
(THE VALUES CORRESPOND TO THOSE OF TABLE I)

FUNCTION	NO. OF SUBJECTS	ΔC-S12		ΔC-S24		ΔR12-S24		ΔR32-S24		ΔR32-R12		ΔR32-C	
		ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF R12	ABS.	IN PER CENT OF C
Heart rate (beats/min.)	32	−19.9†	−36.1	−17.9†	−32.4	11.9†	31.9						
	20	—	—	−17.4	−31.7	12.5	33.3	21.2†	56.5	8.7†	17.4	3.8†	6.9
Range of heart rate absolute	32	−6.4†	−65.2	−6.1†	−64.3	4.2†	123.1						
	20	—	—	−6.5	−66.4	3.9	118.2	7.1*	215.2	3.2*	44.5	0.6	6.1
Range heart rate in per cent of aver. rate	32	−6.6†	—	−5.9†	—	5.3†	—	—	—	—	—	—	—
	20	—	—	−6.5	—	5.0	—	9.1†	—	4.0†	—	2.5	—
Absol. Q-T (x 100)	32	10.3†	28.8	9.3†	25.9	−3.8†	−8.4						
	20	—	—	9.7	26.8	−4.4	−9.6	−6.0†	−13.1	−1.6*	−3.9	3.7†	102.3
Absol. mechan. systole duration (x 100)	32	6.8†	20.9	6.8†	20.9	−2.1†	5.3	—	—	—	—	—	—
$K_{Q\text{-}T}$ (x 100)	32	−0.5	−1.4	−0.7	−1.9	1.8†	5.0						
	20	—	—	−0.6	−1.6	1.5	4.1	2.3†	6.3	0.8	2.1	1.7†	4.5
K_{SYST} (x 100)	32	−2.5†	−7.4	−2.0†	−6.0	2.8†	8.9						

*Statistically significant at 5 per cent level.
†Statistically significant at 1 per cent level.

behind the changes of cycle length. In semistarvation with a lengthening cycle the Q-T interval and the systole duration remained relatively too short, and in rehabilitation with a shortening cycle both intervals remained relatively too long. The validity of the formula for "K" may be questioned, but at least it is useful for description.

In the period from R12 to R32 there was a further decline of the absolute Q-T interval associated with a further increase of the heart rate, but the Q-T interval remained unusually long during the total period of rehabilitation. This is apparent when the values at R32 are compared with the control values, C. At R32, the pulse rate was higher than in the control period C, while the absolute Q-T interval was greater, and not shorter as should be expected. The difference between R32 and C for K_{Q-T} is statistically highly significant. The difference between R32 and C for the heart rate, about four beats, although statistically significant, is so small that all formulas suggested for the relation of the Q-T interval to cycle length would show the same results, since in so narrow a limit the curves of all formulas are practically straight lines. The relative Q-T prolongation is one of the most persistent electrocardiographic changes after semistarvation.

Amplitude Changes.—Tables III and IV show amplitude and axis changes; Table III gives the absolute values and standard deviations, while Table IV gives the absolute and percentage differences and their statistical significance. Values for the QRS complex and T-wave amplitude for Lead III are omitted because the changes in this lead can be inferred from the amplitudes in other leads and the axis as given in Table III. There was a very marked decrease of the P wave, the QRS complex, and the T-wave amplitude in Lead I at S12, while the amplitude of T_2 and Σ_T did not change essentially. The decrease of the QRS amplitude in Lead I is most pronounced, due to a combined effect of QRS axis shift and decrease of QRS amplitude. The decrease of T_1 at S12 is due solely to the right axis shift of the T axis. In the interval from S12 to S24 the amplitudes of P_2, of the QRS complex, and of T_1 continued to decrease at about the same rate as during the first twelve semistarvation weeks. The amplitude of the T wave (T_2 and Σ_T), which was still unchanged at S12, thereafter declined rapidly so that the percentage decrease of R_2, Σ_{QRS}, T_2, and Σ_T was about the same at S24. Changes of Σ_{QRS} and Σ_T could, to a certain extent, be produced by axis changes. Calculation of the manifest potential or the correction factor of Ashman and Byer[11] could be used for a closer estimate of the actual voltage changes. However, the changes of the amplitudes are too great to be possibly accounted for by any axis changes. There was unquestionably a very pronounced and statistically highly significant drop of the actual voltage of all deflections of the electrocardiogram at the end of semistarvation.

The time course of the voltage changes in semistarvation was different from the time course of the interval changes; the interval changes had reached their maximum already at S12, while the amplitude and axis changes reached their maximum deviation at S24. It may be concluded that the interval changes and

TABLE III. AMPLITUDES AND AXIS OF THE ELECTROCARDIOGRAM DURING SEMISTARVATION AND REHABILITATION. MEAN VALUES AND STANDARD DEVIATIONS OF THIRTY-TWO AND TWENTY SUBJECTS

FUNCTION	NO. OF SUBJECTS	CONTROL		S12		S24		R12		R32	
		M	±σ	M	±σ	M	±σ	M	±σ	M	±σ
P wave (mm.) Lead II	32	1.01	0.40	0.68	0.40	0.52	0.34	0.81	0.38	—	—
	20	0.99		—		0.50	—	0.86	—	1.06	0.40
R wave (mm.) Lead I	32	3.75	1.89	2.10	1.05	1.45	0.85	2.44	1.30	—	—
	20	3.24	—	—	—	1.38	—	2.04	—	5.57	2.43
R wave (mm.) Lead II	32	9.91	4.15	8.03	2.30	6.23	2.18	7.09	2.45	—	—
	20	9.30	—	—	—	6.08	—	6.74	—	8.69	2.89
Σ_{QRS}	32	23.49	7.75	18.43	4.10	14.37	4.00	16.65	4.91	—	—
	20	22.60	—	—	—	14.28	—	16.19	—	22.80	4.74
T wave (mm.) Lead I	32	1.70	0.78	1.14	0.51	0.46	0.31	1.20	0.49	—	—
	20	1.74	—	—	—	0.47	—	1.11	—	2.90	0.91
T wave (mm.) Lead II	32	2.73	1.07	2.80	1.32	1.70	1.09	2.92	1.00	—	—
	20	2.88	—	—	—	1.83	—	2.96	—	3.08	1.04
Σ_T (mm.)	32	5.59	2.51	5.60	2.55	3.53	1.92	5.82	1.99	—	—
	20	5.81	—	—		3.79	—	5.92	—	6.89	1.77
QRS axis°	32	68.4	15.9	77.8	9.29	81.6	10.02	69.8	2.06	—	—
	20	70.4	—	—	—	82.4	—	71.2	—	54.2	22.4
T axis°	32	47.5	23.5	65.9	6.57	69.8	23.9	65.2	9.44	—	—
	20	53.4	—	—	—	72.8	—	67.6	—	33.6	17.4

the voltage or axis changes are not closely related to one another and may be due to different causes. Also, there are discrepancies in the time course of amplitude decrease between Σ_{QRS} and R_2 on the one hand and Σ_T and T_2 on the other hand. It seems probable, therefore, that the QRS amplitude changes and the T-wave amplitude changes are also due to different causes.

Although in rehabilitation all amplitudes were increased significantly already at R12, the amplitudes of P_2, R_1, R_2, Σ_{QRS} and T_1 were still well below the control values (C), while the T_2 and Σ_T amplitude had already reached the control values. In the interval from R12 to R32 all amplitudes showed further increases which were highly significant except for T_2. While the major part of the recovery of Σ_{QRS} was completed only in the period from R12 to R32, the major part of the recovery of the T amplitude was completed at R12. While Σ_{QRS} was not significantly different from the control value at R32, Σ_T exceeded the control value by 18.6 per cent, and this difference was statistically significant. This means that discrepancies of the time course between QRS and T changes were observed not only during semistarvation, but also during rehabilitation.

Axis Changes.—Both QRS axis and T axis shifted to the right during semistarvation. This unidirectional shift is of interest, since under many conditions

TABLE IV. AMPLITUDE CHANGES IN THE ELECTROCARDIOGRAM DURING SEMISTARVATION AND REHABILITATION, EXPRESSED AS DIFFERENCES BETWEEN VARIOUS PERIODS, ABSOLUTE AND IN PERCENTAGE OF THE PRECEDING REFERENCE PERIOD (THE VALUES CORRESPOND TO THOSE OF TABLE III)

FUNCTION	NO. OF SUBJECTS	ΔC-S12		ΔC-S24		ΔR12-S24		ΔR32-S24		ΔR32-R12		ΔR32-C	
		ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF R12	ABS.	IN PER CENT OF C
P wave (mm.)	32	−0.33†	−32.6	−0.49†	48.5	0.29†	55.9	—	—	—	—	—	—
Lead II	20	—	—	−0.49	49.5	0.36	72.0	0.56†	111.1	0.20†	23.3	0.07	7.0
R wave (mm.)	32	−1.65†	−44.0	−2.30†	−61.4	0.99†	68.4	—	—	—	—	—	—
Lead I	20	—	—	−1.86	−57.5	0.66	47.8	4.19†	306.5	3.53†	173.2	2.33†	71.9
R wave (mm.)	32	−1.88†	−19.0	−3.68†	−37.2	0.86†	13.8	—	—	—	—	—	—
Lead II	20	—	—	−3.22	−34.6	0.66	10.9	2.61†	42.9	1.95†	28.9	−0.61	−6.6
Σ_{QRS} (mm.)	32	−5.06†	−21.6	−9.12†	−38.8	2.28†	15.9	—	—	—	—	—	—
	20	—	—	−8.32	−36.5	1.91	13.4	8.52†	59.7	6.61†	40.8	0.20	8.9
T wave (mm.)	32	−0.56†	−32.9	−1.24†	−73.0	0.74†	160.7	—	—	—	—	—	—
Lead I	20	—	—	−1.27	73.0	0.64	136.0	2.43†	517.2	1.79†	161.1	1.16†	66.7
T wave (mm.)	32	0.07	2.5	−1.03†	−37.7	1.22†	71.8	—	—	—	—	—	—
Lead II	20	—	—	−1.05	−36.5	1.12	60.8	1.25†	68.4	0.12	4.1	0.20	6.9
Σ_T (mm.)	32	0.01	0.2	−2.06†	−36.9	2.30†	65.2	—	—	—	—	—	—
	20	—	—	−2.02	−34.8	2.13	56.3	3.10†	81.7	0.97*	16.4	1.08*	18.6
QRS axis°	32	9.4†	—	13.2†	—	−11.8†	—	—	—	—	—	—	—
	20	—	—	12.0	—	−11.8†	—	−28.2†	—	−17.0†	—	−16.2	—
T axis°	32	18.4†	—	22.3†	—	−4.6	—	—	—	—	—	—	—
	20	—	—	19.4	—	−5.2	—	−39.2†	—	−34.0†	—	−19.8†	—

*Significant at the 5 per cent level.
†Significant at the 1 per cent level.

QRS and T axes change in the opposite direction. The changes of the T axis were greater than the changes of the QRS axis, but both were statistically highly significant. It appears that a change of the direction of repolarization occurred during semistarvation. The axis changes were continuous during this period. There was no significant correlation between QRS-axis and T-axis changes at S24.

In the rehabilitation period, both QRS axis and T axis shifted back to the left. While the QRS axis attained the control values at R12, the T axis was still much closer to the S24 values; in fact, the changes of the T axis ($\triangle$R12-S24) were not significant, in contrast to the highly significant changes of the QRS axis.

In the period from R12 to R32, the QRS axis, and to a greater extent the T axis, continued to shift toward left. At R32, the QRS axis and especially the T axis were shifted to the left as compared to the control values and these differences were statistically highly significant.

Fig. 1 shows the changes during starvation and rehabilitation of a few fundamental functions: average heart rate and range of variability of heart rate, R_2 and T_2 amplitudes, and QRS and T axes. For the periods C to R12, the values of the total group of thirty-two subjects were taken, and for the period R32 the values of the twenty subjects were used, with a correction for the absolute differences of the control values between both groups. The discrepancies in the time course between the heart rate changes and the amplitude changes are obvious.

Fig. 2 shows the typical sinus bradycardia, right axis shift, and decrease of the P, QRS, and T amplitudes during starvation on one of our subjects. The changes are regressive at R12. While the electrocardiograms of all subjects (except one with a left axis shift bordering on left ventricular preponderance) were within normal limits before the experiment started, the majority (75 per cent) would have to be classified as abnormal at S24 because of low voltage of the QRS complex and T waves.

Effect of the Caloric Level in the Rehabilitation Period.—In the preceding analysis of our results, the effect of rehabilitation was discussed without differentiation of the four caloric groups; these were spaced in intervals of 400 calories and designated in increasing order as Z, L, G, and T. As has been shown, the recovery of most electrocardiographic functions was far from complete at R12; in fact, the recovery of many functions was only slight, although statistically significant. Therefore, no clear-cut differentiation of the different caloric groups could be expected at that time, while later, after the twelfth week, the diet was no longer controlled. However, a complete statistical analysis was made, and a statistically significant differentiation of caloric groups was found for the following items: duration of mechanical systole, $K_{Q\text{-}T}$, R wave in Leads I and II, Σ_{QRS}, T wave in Leads I and II, Σ_T, and T axis.

The differentiation was significant only in the extreme groups, either Group Z (for instance, mechanical systole duration) or Group T (for instance, R_1) was

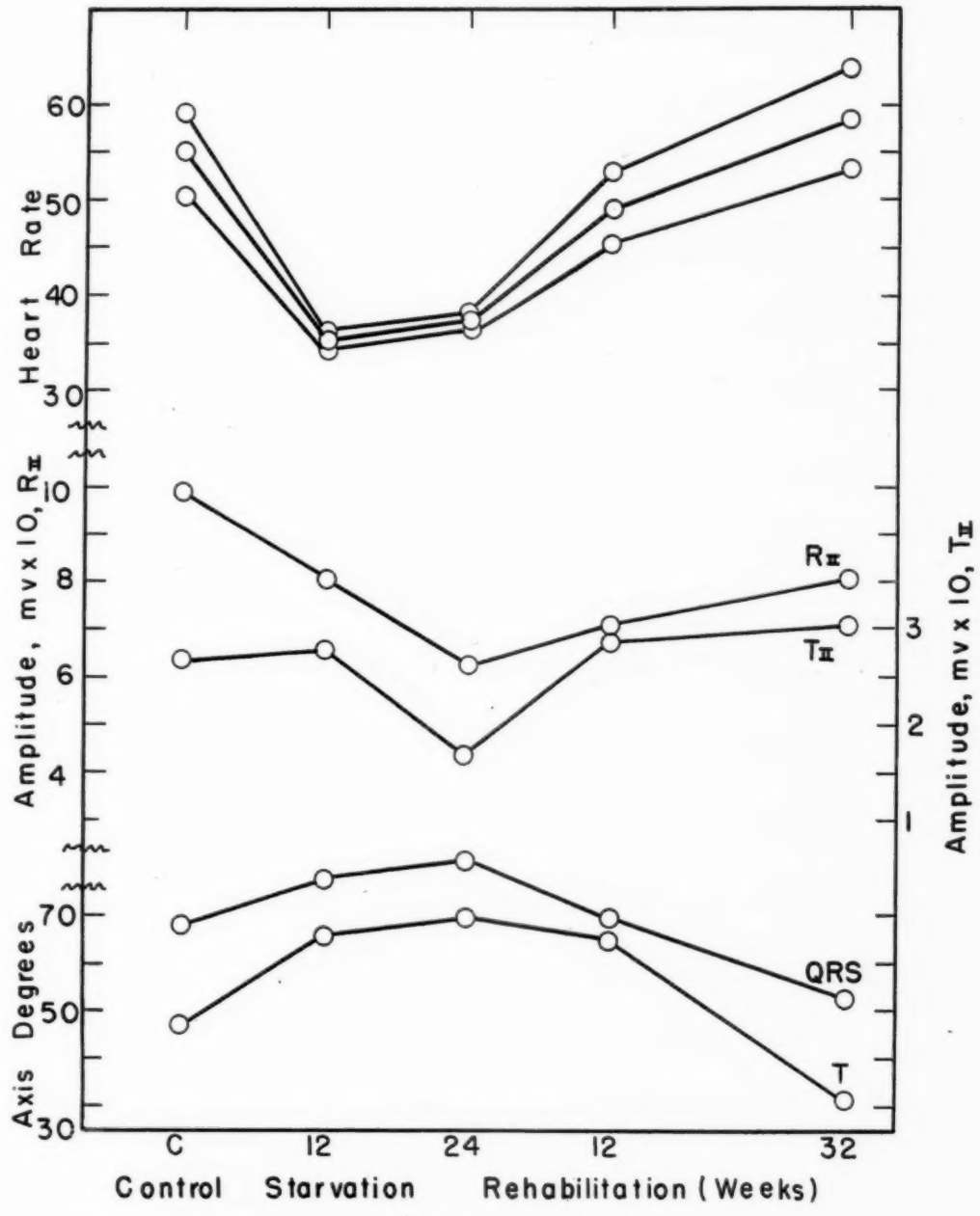

Fig. 1.—Changes of heart rate, R_2 amplitude, T_2 amplitude, QRS axis, and T axis during starvation and rehabilitation. The upper part of the graph shows the changes of the average heart rate (middle curve) and the variability of the range of the heart rate, calculated from the longest and shortest R-R interval (lower and upper curve). The middle part of the graph shows the amplitude changes in mv. x 10 of the R wave and T wave in Lead II. The lower part of the graph shows the changes of the QRS axis and T axis.

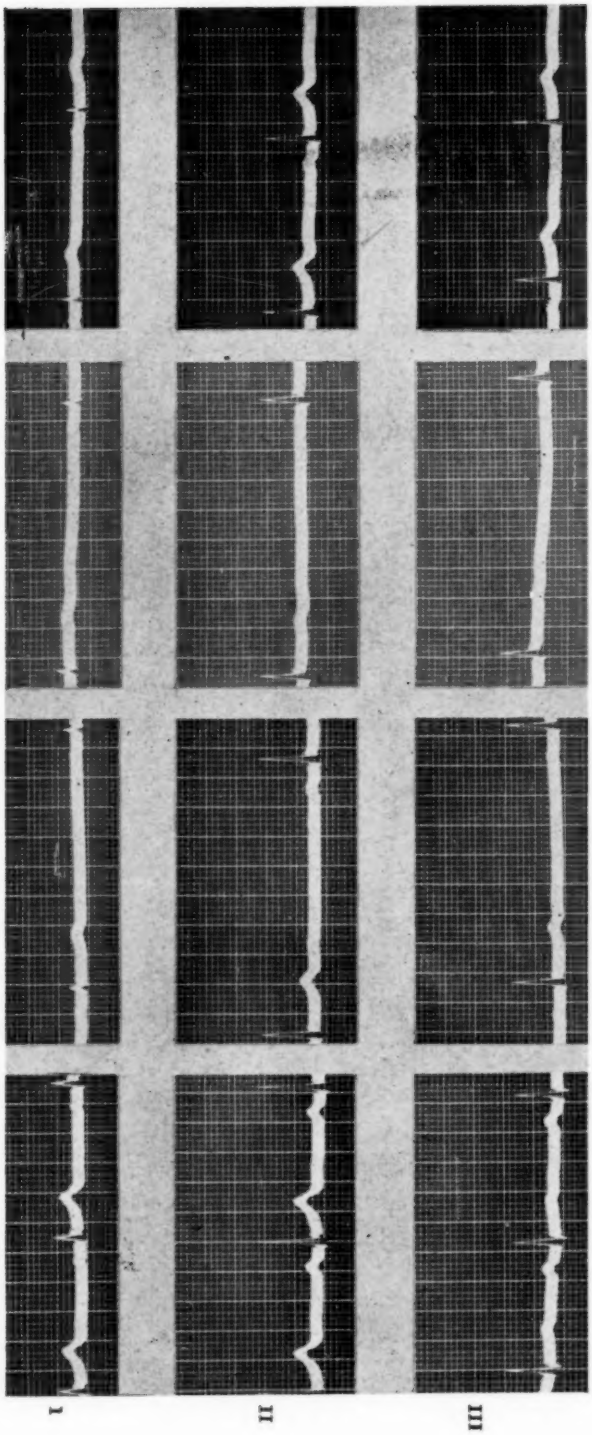

Fig. 2.—Electrocardiograms of a typical subject during control, semistarvation, and after twelve weeks of rehabilitation.

significantly different from the other three caloric groups, or the extreme groups (T versus Z) were significantly different, or the combined groups G+T versus L+Z were significantly different.

There was no significant difference of any electrocardiographic function in regard to high and low protein intake or high and low vitamin intake. It seems that the duration of mechanical systole and the R_1 amplitude might be especially useful for differentiation of caloric groups in rehabilitation.

The Effect of Maximum Inspiration.—One of the most pronounced changes during semistarvation is the sinus bradycardia. While the slowing of the heart rate may be regarded as an adaptation to the decreased metabolic rate, the underlying mechanism was not clear when the experiment was started. The effect of a maximal voluntary inspiration was used as a possible approach to study the pulse rate regulation. In the early phase of the maximal inspiration, the acceleration of the heart rate, probably due to sympathetic stimulation, was observed in all subjects, while a retardation below the resting pulse rate in the late phase of maximal inspiration, obviously a vagus effect, was present only in eighteen subjects. The analysis of the late effects of maximal inspiration was made only in those eighteen subjects who showed a definite vagus effect; no change of vagus stimulation during semistarvation could be expected if such an effect were absent in the control period (C).

Table V shows the effect of the early and the late phase of maximal inspiration on the heart rate, on $K_{Q\text{-}T}$, and K_{SYST}. The values show the changes produced by the maximal inspiration, as compared with the values at rest. The

TABLE V. RESPONSE TO MAXIMUM INSPIRATION (MEAN VALUES, DIFFERENCES, AND STATISTICAL SIGNIFICANCE)

FUNCTION	NO. OF SUBJECTS	C	S24	R12	Δ S24-C	Δ R12-24	PHASE OF MAX. INSPIR.
Heart rate	30	21	14.5	16.8	−6.5†		Early
Heart rate	32		14.5	16.5		2.0	Early
Heart rate	18	−7.1	−1.9	−3.7	5.2†	−1.8*	Late
Range of heart rate, difference rest-max. inspir.	30 32	24.7	15.3 15.3	18.4 19.4	−9.4†	4.1	Total duration
$K_{Q\text{-}T}$ (x 100)	30	73.5	63.8	55.8	−9.7	−8.0	Early
$K_{Q\text{-}T}$ (x 100)	31	−26.2	−14.5	−35.3	+11.7*	−20.8†	Late
K_{SYST} (x100)	28	−26.9	−15.6	−32.2	+11.3*	−16.6†	Late
Mech. syst. dur. (x 100)	28	−1.53	−0.86	−1.25	+0.67*	− 0.39	Late

*Significant at the 5 per cent level.
†Significant at the 1 per cent level.

initial acceleration, as well as the late retardation effect, was much less pronounced at S24 as compared to C, and this decrease was statistically highly significant. During twelve weeks of rehabilitation, there was no significant change in the initial acceleration, while the retardation effect became more pronounced again, so that the difference of the response Δ R12-S24 was significant at the 5 per cent level. However, the retardation response was still definitely less than it had been before starvation (C).

The range of heart rate under the influence of maximum inspiration was calculated as the difference between the shortest and longest cycle, and was compared with the variability range during rest (Table I). Since both initial acceleration and late retardation decreased in semistarvation, the range of the heart rate showed a corresponding decrease at S24; the recovery was far from complete at R12.

It is known that the adaptation of the Q-T interval to rapid changes of the cycle length is incomplete, so that pronounced changes of $K_{Q\text{-}T}$ occur. However, this coefficient is still useful for an analysis of a possible change in the mechanism of Q-T cycle adaptation. In calculating the effect of the late phase of respiration, the values of all subjects were used.

The increase of $K_{Q\text{-}T}$ in the early phase of maximum inspiration, above the resting values of Table I, did not change significantly during semistarvation and rehabilitation. The decrease of $K_{Q\text{-}T}$ and K_{SYST} in the late phase of maximal inspiration, indicating a lag of adaptation to the increasing cycle length, was much smaller at S24. This trend was reversed again in rehabilitation, even overshooting the control values (C) at R12. The changes were statistically significant. The mechanical systole could not be determined at the early phase of maximal inspiration because of the interference of the noise produced by the inspiration. The fact that the values at R12 overshot the control values (C), while the recovery of the heart rate was still far from complete at that time, suggests that there is a direct effect of semistarvation on the response of Q-T and mechanical systole to maximum inspiration, which is independent, to a certain extent, of the response of the heart rate. This is borne out by analysis of the absolute systole duration. The response of the whole group was significantly less at S24, as shown in Table V. The total group was divided according to the presence of a vagus retardation effect on the heart rate in the late phase of maximal inspiration. The mean values of the mechanical systole for fifteen subjects with retardation were -1.53, -0.93, and -1.33 for the periods C, S24, and R12, respectively. The mean values for thirteen subjects without retardation of the heart rate were -1.53, -0.73, and -0.14, respectively. There were no significant differences between the group with retardation and the group without retardation.

Occasional Observations.—Some interesting occasional observations were made in a few subjects. In Subject 102 (first subject of Fig. 3), the P wave became slightly negative during the late phase of maximal inspiration (indicated by the

signal) with shortening of the P-R interval after four weeks of semistarvation. Later, the P wave disappeared entirely at the end of maximal inspiration, and this phenomenon remained the same also during twelve weeks of rehabilitation.

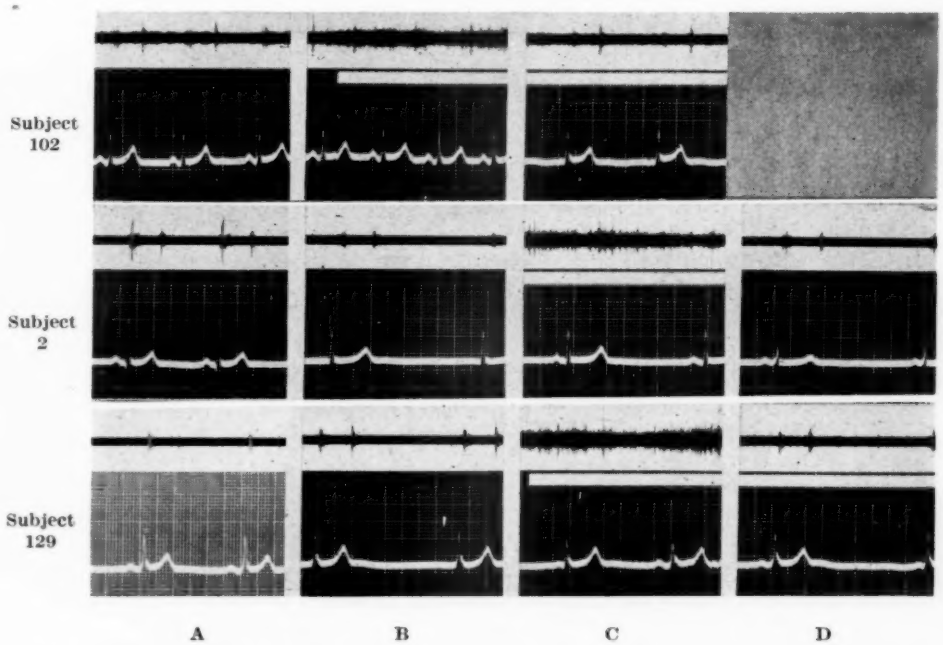

Fig. 3.—Subject 102, fifth week of starvation. *A* = Lead II, before maximum inspiration. *B* = Lead II, early phase of maximum inspiration. Increased heart rate, no change of P wave. *C* = Lead II, late phase of maximum inspiration: nodal rhythm.

This phenomenon remained the same during semistarvation and rehabilitation.

Subject 2. *A* = Control period; Lead II at rest. Sinus rhythm. *B* = Lead II, thirteenth week of starvation, at rest before maximum inspiration. Nodal rhythm. *C* = Same E.C.G., same lead, during late phase of maximum inspiration. A P wave has appeared, indicating re-establishment of sinus rhythm. *D* = Sinus rhythm is still present in the subsequently taken Lead III.

Subject 129. *A* = Control period, Lead II; normal sinus rhythm. *B* = Fifth week of starvation, Lead II, before maximum inspiration. Nodal rhythm. *C* = Already, in the early phase of maximum inspiration, a P wave appears which is present only during the maximum inspiration. *D* = Late phase of maximum inspiration. The P-R interval in the last beat is shortened to 0.1 second; in the subsequent beats no P wave is present.

In Subject 2, just the opposite phenomenon occurred. Beginning at S13, the sinus rhythm was replaced by nodal rhythm (second and third subjects of Fig. 3), but maximal respiration produced a transitory restoration of the sinus rhythm. In Lead III, taken after Lead II, the sinus rhythm was still present. Also, in Subject 129, the normal sinus rhythm (third subject, Fig. 3,*A*) was replaced by a nodal rhythm (third subject, Fig. 3,*B*) as early as S5. In the early phase of maximal respiration, a small P wave with a short P-R interval (0.09 second) appears in the first beat (third subject, Fig. 3,*C*) while in the second beat the P wave is of about normal (prestarvation) amplitude with a P-R interval of 0.19 second. In the late phase of maximal inspiration, the P-wave amplitude and P-R interval decrease again; the P-R interval in the first beat of Fig. 3 (third

subject, *D*) is 0.16 second, in the second beat 0.10 second, indicating nodal rhythm again. Although the effect of maximum inspiration is similar in both subjects, the sinus rhythm is restored for a much shorter time in Subject 129, in fact, it is restricted to the duration of the maximum inspiration. These were the only subjects in whom semistarvation produced a nodal rhythm.

DISCUSSION

Relation to Previous Records.—Our results are confirmatory to the general observations of decreased QRS and T-wave amplitude in famine areas, but the latter have only the character of occasional observations in patients, while in our experiments quantitative relationships were obtained under controlled conditions.

Our results disagree with the reports of Cardozo and Eggink[4] and of Ellis[5] that the Q-T interval is lengthened in relation to the cycle length. The only explanation we are able to offer for the discrepancy is the possibility that these authors happened to investigate another (and generally more advanced) phase of semistarvation.

Amplitude Changes.—The decrease of the QRS and T-wave amplitudes is probably the most significant change of the electrocardiogram in starvation. It may be due to the following causes:

1. *Decrease of Heart Size*: The decrease of the amplitudes was accompanied by a very marked decrease of the heart size as determined by teleroentgenograms and roentgenkymograms. These results are presented elsewhere[1]; it may be mentioned that there is also good evidence from autopsy material that the heart weight decreases in semistarvation much in proportion to the loss of body weight.[12-14] Since in the hypertrophic heart the QRS amplitude is, as a rule, increased, it might seem logical to assume that a decrease in an atrophic heart would be explained on this basis alone. However, this assumption should not be made without reservations, since secondary changes in the hypertrophic heart, which are absent in the atrophic heart, might be contributory.

2. *Myocardial Degeneration*: There is evidence of widespread degenerative histologic changes in the hearts of starved animals[15-17] which has been confirmed recently by Pollack[18] in human autopsy material.

3. *Decreased Metabolic Rate*: Although there is no outright correlation between QRS amplitude and the basal metabolic rate, both QRS and T amplitudes are usually decreased in hypothyroidism and have a tendency to be increased in hyperthyroidism. The average basal metabolic rate of our group decreased 37 per cent during semistarvation, and at R12 was still only 82 per cent of the prestarvation control.

4. *Fluid Accumulation in Chest or Pericardium*: Although twenty-eight out of thirty-two of our subjects showed clinical edema during semistarvation there was no evidence to indicate an accumulation of fluid in the chest or pericardium.

Axis Changes.—The right axis shift of the QRS complex was probably due to positional changes; a smaller heart tends to assume a more vertical position. A right axis shift of the anatomic axis was obvious in the x-ray studies.[1] However, there was no exact correlation between the right axis shift of the anatomic axis and the QRS axis; this discrepancy might be due to the fact that the x-ray studies were made in the standing position, while the electrocardiograms were taken in the supine position.

It is also possible that the right axis shift of the QRS axis is due to a relative right ventricular preponderance or to a change in the pathway of excitation. A relative right ventricular preponderance could be produced by a greater degree of atrophy in the left ventricle; there are no data available to support or to contradict such assumption. In this connection, it is interesting that in Tur's material right axis shift was more common in the advanced cases than it was in the milder cases. The main reason for the overshooting of the left axis shift in rehabilitation is probably mechanical: all men were fatter, particularly in the abdominal region, at R32 than they were at C; the increased volume of the abdominal organs would explain a position of the axis farther to the left.

Heart Rate.—The slow heart rate in semistarvation is referable to a sinus bradycardia in most cases, but our material shows that in exceptional cases nodal rhythm occurs. The occurrence of nodal rhythm would be compatible with the assumption that the slow heart rate in semistarvation is due to increased vagus tone. Schiff[19] reported that atropine (0.5 to 0.75 mg.) promptly abolished starvation bradycardia for a transitory period, but Schittenhelm and Schlecht[20] found no effect whatever with 1.0 mg. of atropine. We found not only the late vagus effect, but also the early sympathetic acceleration of the heart rate to be decreased in maximum inspiration. Since both vagus and sympathetic response are diminished, the slow heart rate may be due to both increased vagus tone and loss of sympathetic tone. This would agree with Hoesslin's[21] observations of the absence of emotional pulse rate changes in semistarvation and with our findings of the decreased range of variability.

Jordan's[22] observation that the initial digitalis retardation of the heart rate fails to appear in starving dogs is an interesting corroboration of our results. Statkewitsch's[23] findings of extensive pathologic changes in the cardiac ganglia of rabbits in advanced inanition might be regarded as histologic evidence for the loss of vegetative regulation which would only be very slowly reversed in rehabilitation.

Significance of Our Results for Heart Pathology in Malnutrition.—Except for the beriberi heart, the condition of the heart in states of malnutrition has found little attention in clinical medicine. In several recent textbooks of cardiology,[24-29] no mention is made of the importance of the nutritional state for cardiac pathology. Vaquez[30] recognized the theoretical importance of nutritional effects on the condition of the myocardium, but he was inclined to believe that the effect is insignificant. Although in general there is little correlation between electrocardiographic findings and the functional state of the heart,

the occurrence of significant changes in most electrocardiographic items during semistarvation cannot be ignored. It seems safe to conclude that they indicate myocardial changes. The implications of the present results would be that prolonged semistarvation produces a deterioration of the state of the myocardium, which might be functionally compensated for a time. However, the compensation might break down under conditions of additional stress. In the present study such stress conditions were excluded, but they might well arise under less well-protected conditions. In connection with this, it is interesting to note that one of our subjects suddenly became decompensated in the early rehabilitation period; the heart became enlarged and the venous pressure rose abruptly. Treatment with bed rest, reduced food intake, and diuretics restored the patient within one week. The reason the decompensation appeared in the rehabilitation period might be the increased circulatory load due to sharply increased food ingestion and greater activity.

SUMMARY

1. In thirty-two normal subjects, electrocardiograms were taken at regular intervals during a control period of three months, during a semistarvation period of six months in which a 24 per cent weight loss was produced, and during a controlled rehabilitation period of twelve weeks. In twenty subjects, electrocardiograms were taken also after thirty-two weeks of rehabilitation, the last twenty weeks being on a freely chosen diet.

2. During semistarvation, statistically highly significant changes occurred in most electrocardiographic items, and the electrocardiograms became clinically abnormal in the majority of subjects.

3. There was pronounced slowing of the heart rate, and its variability range decreased both relatively and absolutely so that the heart rate was more regular in semistarvation. These changes reached their maximum at the twelfth week of semistarvation, and recovered slowly during rehabilitation.

4. Q-T interval and mechanical systole duration increased during semistarvation and shortened again during rehabilitation, but these changes lagged behind the simultaneous changes of the cycle length in both directions, so that $K_{Q\text{-}T}$ and K_{SYST} changed accordingly.

5. The amplitudes of all deflections (P wave, QRS complex, and T wave) decreased continuously and very considerably during semistarvation and recovered slowly during rehabilitation.

6. During semistarvation, there was a marked right axis shift of the QRS axis and even more so of the T axis, so that the angle between both axes was diminished. During rehabilitation, both QRS axis and T axis moved to the left, overshooting the original prestarvation position at the thirty-second week of semistarvation.

7. Most electrocardiographic items were only partially recovered during twelve weeks of rehabilitation, but were back to the control values within thirty-

two weeks, several functions (heart rate, R_1, Σ_T, QRS axis, T axis) overshooting the control values subsequently.

8. There was a discrepancy in the time course of changes between interval and amplitude changes, and between QRS complex and T-wave changes.

9. There was no correlation between QRS axis changes and anatomic axis changes, or between QRS axis and T axis, although all changed in the same direction.

10. A statistically significant differentiation of the groups receiving different caloric levels during rehabilitation was obtained in the following items: systole duration, K_{QT}, R_1, R_2, Σ_{QRS}, T_1, T_2, Σ_T, and T axis.

11. Before semistarvation, voluntary maximal inspiration produced an initial acceleration of the heart rate in all subjects, which was followed by a late retardation in eighteen subjects.

12. During semistarvation, the effect of maximal inspiration was diminished in respect to both initial acceleration and late retardation. During twelve weeks of rehabilitation, only the late retardation was restored.

13. The decrease of K_{QT} and K_{SYST} in the late phase of maximal inspiration was significantly less pronounced at the end of semistarvation, and this effect was, to a certain degree, independent of the changes in the heart rate.

14. While the slow heart rate in semistarvation, as a rule, was due to sinus bradycardia, in two subjects nodal rhythm was observed; this was temporarily restored to sinus rhythm during maximum voluntary inspiration.

ACKNOWLEDGMENT

This wor would not have been possible without the loyal cooperation of the volunteers from Civilian Public Service who acted as subjects, and others who gave assistance. Mr. Arthur Butler made the detailed measurements of the electrocardiograms. Dr. Howard Alexander and Mr. Richard Seymour supervised the statistical work. Most of the electrocardiograms were taken by Miss Angie Mae Sturgeon.

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RESPONSE OF PERSONS WITH AND WITHOUT INTRAVASCULAR THROMBOSIS TO A HEPARIN TOLERANCE TEST*

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IN NOVEMBER, 1942, de Takats and Gilbert[1] presented a paper on use of the response to heparin as a test of the clotting mechanism of the blood. In July, 1943, de Takats[2] published further data on this subject and gave the name "heparin tolerance" to the test. Without detracting from the possible value and importance of this approach to the study of blood coagulability in health and disease, we wish to point out that the exact technique used by these authors appears to be open to certain criticisms. First, a relatively small amount of heparin was used, thus perhaps limiting the range of response to the anticoagulant. Second, since capillary blood was tested, possibly the presence of variable amounts of tissue thromboplastin limited the accuracy of comparable determinations of coagulation time. Third, the coagulation test used was that of breaking blood-filled capillary tubes, which is not considered an accurate standard coagulation test. Fourth, the differences in the time given for normal and abnormal reactions were small and possibly within the limits of probable error of the method.

PURPOSE OF STUDY

Because of the tremendous interest during the last few years in the factors responsible for thrombosis and embolism, the work reported in abridged form herein was undertaken to substantiate de Takats and Gilbert's major premise by utilization of a slightly different technique. After the beginning of this work and before its completion, de Takats and co-workers[3-5] published other papers on the effect of administering various drugs and of nervous regulation on the clotting mechanism as indicated by the results of the heparin tolerance test. Earlier, Macht[6] had pointed out the effect of administration of certain drugs on the response to injection of heparin. Since our primary aim was to measure the response to the heparin tolerance test in normal individuals and in those with conditions associated with thrombosis, we have not attempted to investigate the numerous implications suggested by the papers to which we have just referred.

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*Abridgment of thesis submitted by Dr. Hagedorn to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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METHODS

We decided to administer intravenously an arbitrary dose of 25 mg. of heparin in 2.5 c.c. of liquid and to study the effect on the coagulation time in different individuals. The coagulation time was determined by a slight modification of the method of Lee and White[7]; that is, by the inversion, every thirty seconds, of a 10 by 75 mm. Wassermann-type glass tube containing 1 c.c. of blood withdrawn from a vein of the arm. The coagulation time was determined before the injection of the heparin intravenously and at intervals of ten, twenty, thirty, forty, and sometimes fifty, sixty, and ninety minutes after injection. All tests of the coagulation time were done at the usual temperature of the hospital room.

The fifty control subjects were adult men and women between the ages of 18 and 62 years and were all apparently healthy. For the most part, the seventy patients were those suffering from peripheral vascular disease with old or recent intravascular thrombosis. For convenience, the patients were separated into five categories: (1) those with thromboangiitis obliterans; (2) those with arteriosclerosis obliterans; (3) those with thrombophlebitis, old and recent; (4) those with conditions associated with types of thrombosis other than those of the preceding three categories; and (5) those suffering from miscellaneous diseases

TABLE I. COAGULATION TIME, IN MINUTES, OF THE BLOOD OF THE FIRST ELEVEN CONTROL SUBJECTS BEFORE AND AT STATED INTERVALS AFTER THE INTRAVENOUS INJECTION OF 25 MG. OF HEPARIN

SUBJECT	BEFORE INJECTION	MINUTES AFTER INJECTION OF HEPARIN						
		10*	20	30	40	50	60	90
1	8½	54½	52	36	26		26	18
2	7½	62	37	20	9			
3	6½	94	24½	20½	18½			
4	4½	62	38½		15		13½	
5	6½	59	15½	9	8½			
6	6½	64	50	20	14	8	7½	
7	7	74	50	20	18	12	8	
8	7	58	46	30	18	11	9	
9	6½	54½	47	24	12	9½		
10	7	90	50	55	20		18	
11	8	110	24½	20	9½			

*Note the maximal response at ten minutes after the intravenous injection of 25 mg. of heparin in 2.5 c.c. of solution.

not associated with known thrombosis. In the fourth category were two patients with simple arterial thrombosis, both of whom made no response to the intravenous injection of heparin, and three patients with postoperative pulmonary infarction, two of whom gave no response and one of whom gave a normal response to administration of heparin.

After heparin tolerance curves had been determined on eleven normal subjects and thirty-seven patients, it was obvious that the maximal response to heparin observed at any of the ten-minute intervals was the one which occurred ten minutes after intravenous injection (Table I). In all subsequent tests, therefore, the coagulation time was determined only before (control) and ten minutes after the intravenous injection of heparin. Thus, only two venepunctures on each subject were necessary instead of the five or six venepunctures previously required, a definite simplification of the procedure.

De Takats and co-workers classified the responses of the blood of different individuals to the intravenous injection of heparin into four groups as follows: normal, hyperactive, hypoactive, and no response. We have classified our results similarly (Fig. 1). If the coagulation time of the sample of blood withdrawn ten minutes after the injection of 25 mg. of heparin was less then ten minutes, the result of the test was considered as indicating no response to heparin; if the coagulation time was ten to forty minutes, the response was considered hypoactive; if it was forty to ninety minutes, the response was considered normal; and if it was more than ninety minutes, the response was considered hyperactive.

RESULTS

The coagulation time of the blood of three normal persons determined before and after the intravenous injection of 25 mg. of heparin did not vary significantly from day to day (Table II). Similar results were obtained in the study

TABLE II. COAGULATION TIME, IN MINUTES, OF THE BLOOD OF THREE NORMAL SUBJECTS DETERMINED ON DIFFERENT DAYS BEFORE AND TEN MINUTES AFTER THE INTRAVENOUS INJECTION OF 25 MG. OF HEPARIN

SUBJECT	FEB. 22, 1945		MARCH 5, 1945		MARCH 9, 1945		APRIL 1, 1945		APRIL 11, 1945	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1	4½	56	6½	63	7½	54	5	60	5½	64
2	5½	51	6	59			5	48	5½	64
3	7	48	7	44	7	52			7	57

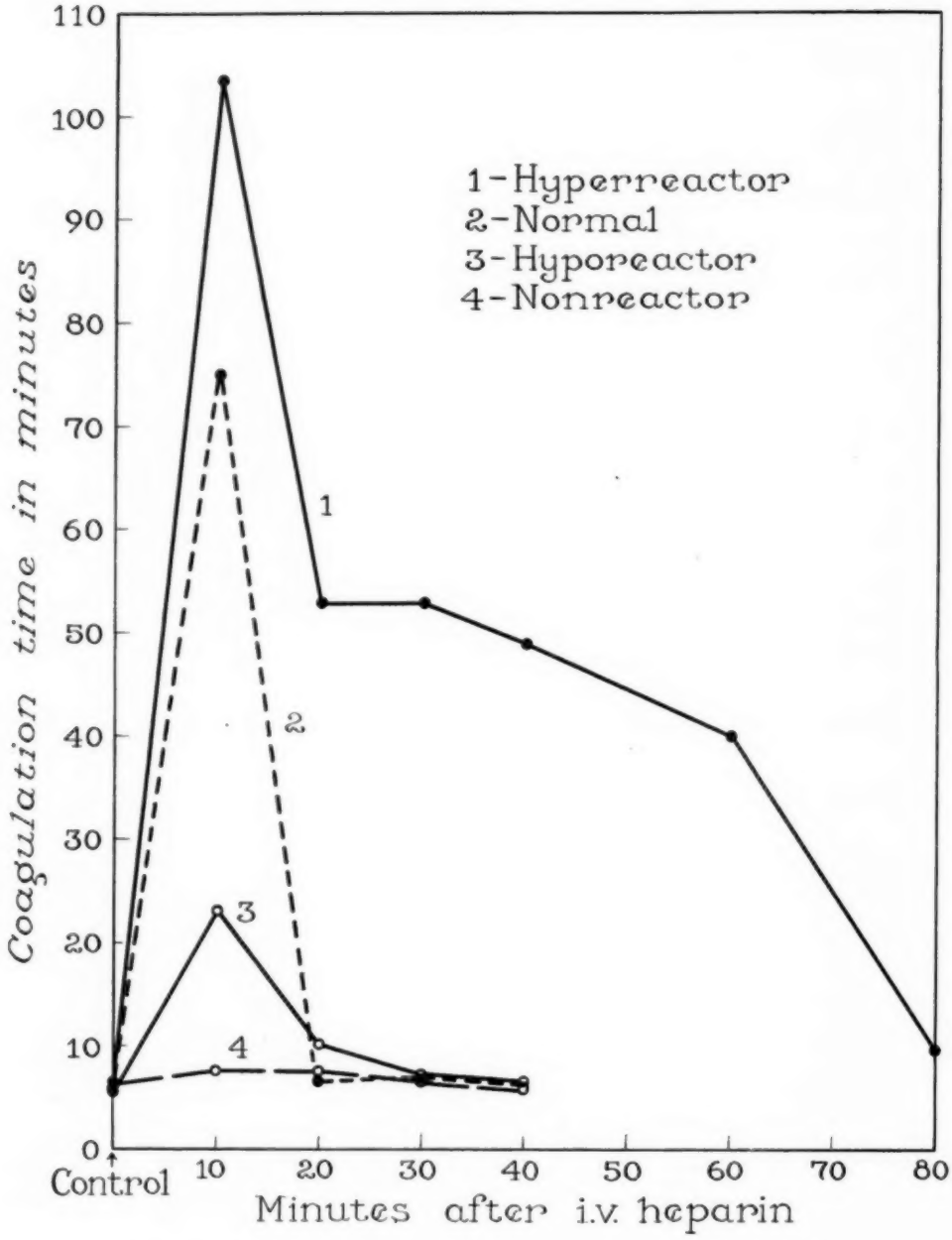

Fig. 1.—Heparin tolerance curves showing the four types of responses obtained.

of nine patients. The results were consistent. Results on one of these patients are shown in Fig. 2. An individual who gave no response to heparin on one day also gave no response to heparin when the test was repeated on another day; an individual who gave a hypoactive response on one day also gave a hypoactive response when the test was repeated a few days later. In contrast, the response to the heparin tolerance test varied considerably among different persons who were suffering from the same disease (Fig. 3).

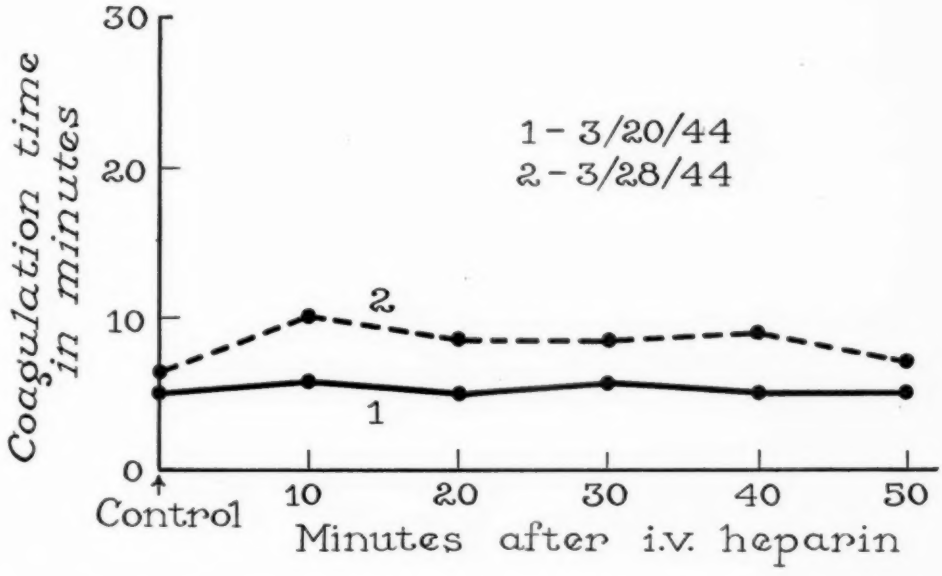

Fig. 2.—Thromboangiitis obliterans: heparin tolerance curves for the same patient on different days.

Two patients to whom heparin was given intravenously experienced mild hypersensitivity to the drug. Neither gave a hyperactive response in terms of the classification of de Takats and co-workers. The first was a patient with chronic pernio whose sensitivity was manifested by a generalized erythema, feeling of giddiness and suffocation, dyspnea, tachycardia, sudden cough, and borborygmus. He had a sensation of coldness of the hands and feet. The manifestations of hypersensitivity lasted less than ten minutes. The heparin tolerance test was carried out as usual; the response with regard to coagulation time was normal. The second patient had chronic rheumatic endocarditis with mitral stenosis, auricular fibrillation, and an acute occlusion of the right brachial artery. This patient's hypersensitivity was manifested by mild pain in the middle part of the back and a "funny feeling." There were no objective signs. These manifestations lasted only three or four minutes. This patient made no response to the injection of heparin in so far as the coagulation time was concerned.

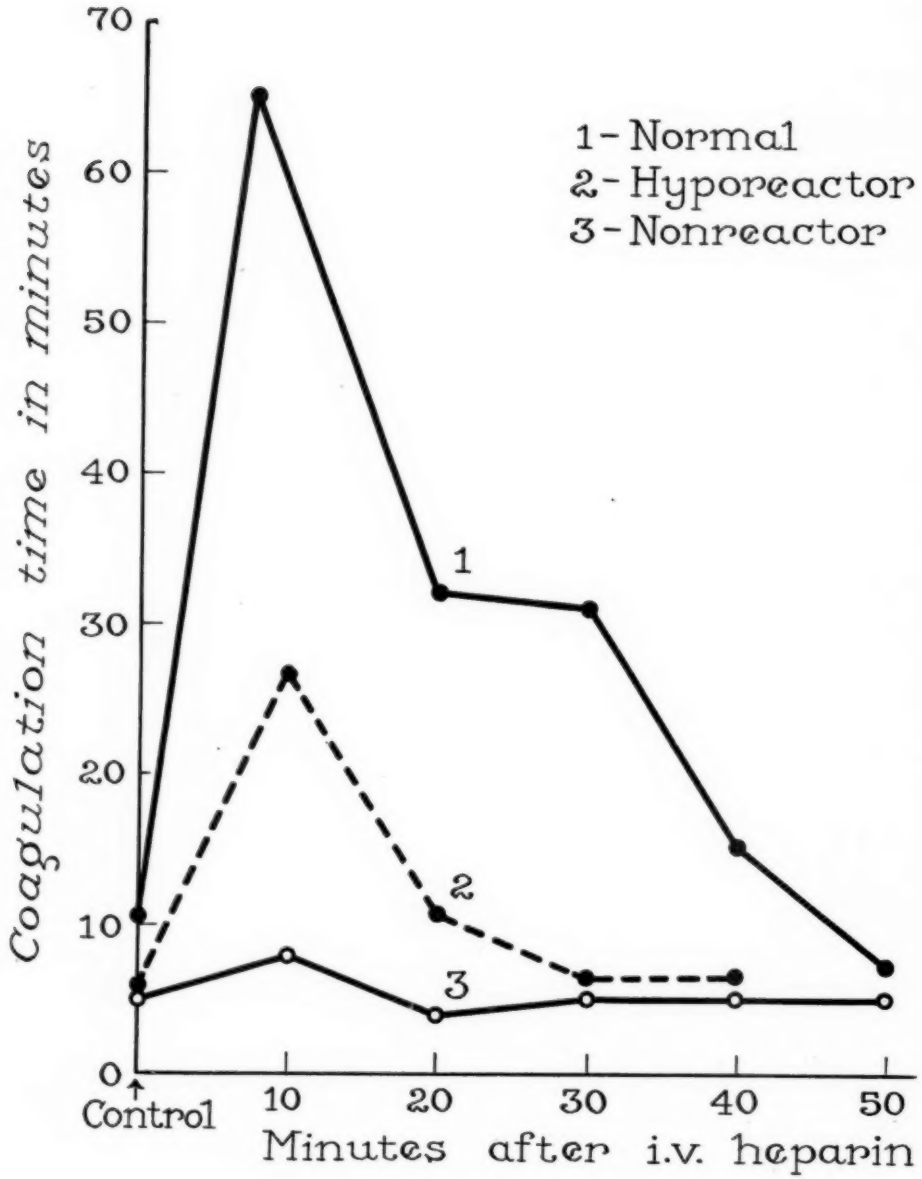

Fig. 3.—Arteriosclerosis obliterans: heparin tolerance curves showing responses in different patients with arterial thrombosis.

The comparative results of our study of the heparin tolerance test in fifty control subjects and in seventy patients with and without evidence of intravascular thrombosis are shown in Table III.

TABLE III. SUMMARY OF THE RESULTS OF A STUDY OF THE HEPARIN TOLERANCE TEST IN SIXTY-ONE PATIENTS WITH EVIDENCE OF INTRAVASCULAR THROMBOSIS, IN NINE PATIENTS WITHOUT EVIDENCE OF INTRAVASCULAR THROMBOSIS, AND IN FIFTY NORMAL SUBJECTS

	TOTAL TESTED	HYPER-REACTORS		NORMAL REACTORS		HYPO-REACTORS		NON-REACTORS	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Patients with thrombo-angiitis obliterans	22	0		5	23	6	27	11	50
Arteriosclerosis obliterans	18	0		7	39	8	44	3	17
Thrombophlebitis (old and recent)	11	0		5	46	3	27	3	27
Other conditions associated with thrombosis	10	0		2	20	1	10	7	70
Patients with evidence of intravascular thrombosis—total	61	0		19	31*	18	30	24	39
Patients without evidence of intravascular thrombosis	9	1	11	5	56	3	33	0	
Normal subjects	50	2	4	47	94	1	2	0	
Patients without evidence of intravascular thrombosis and normal subjects combined	59	3	5	52	88	4	7	0	

COMMENT

We cannot say whether the heparin tolerance test as applied by us can be used to determine the presence or absence of a tendency to intravascular thrombosis, but we believe there is significance in the relatively high incidence of nonreactors and hyporeactors among the patients who had intravascular thrombosis. However, further study of a larger series of cases of thrombosis of various types is indicated. Since the procedure for doing the test is time consuming, a simplification of the method would be desirable.

As previously stated, all coagulation tests were done at the ordinary temperature of the hospital room. They were all made by the same individual, who used the same technique and the same set of equipment each time. Therefore, we believe that the results obtained are comparable. We admit that more accurate standardization is desirable[8-10] but often not practicable.

SUMMARY

The coagulation time of 1 c.c. of venous blood placed in a 10 by 75 mm. Wassermann-type glass tube and inverted every thirty seconds has been obtained on fifty control subjects and seventy patients before and after the intravenous injection of 25 mg. of heparin in 2.5 c.c. of liquid.

The results of the determinations of coagulation time on samples of venous blood withdrawn at ten-minute intervals for variable periods indicated that the maximal response to the intravenous injection of heparin occurred ten minutes after injection.

Of the individuals without evidence of intravascular thrombosis, including the control subjects, 5 per cent were hyper-reactors; 88 per cent, normal reactors; 7 per cent hyporeactors, and none were nonreactors.

Of the individuals with evidence of intravascular thrombosis (categories 1 to 4 in Table III), none were hyper-reactors, 31 per cent were normal reactors, 30 per cent were hyporeactors and 39 per cent were nonreactors.

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HEREDITARY DISTURBANCE OF CHOLESTEROL METABOLISM: A FACTOR IN THE GENESIS OF ATHEROSCLEROSIS

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THE high incidence of coronary atherosclerosis and cardiac infarction among patients with hereditary xanthomatosis is well known. We have recently reported on the relative frequency of hypercholesterolemia, xanthoma tuberosum and tendinosum, arcus senilus, xanthelasma, and coronary artery disease, and have studied sixty-four individuals with this metabolic disorder.[1] Xanthoma families are by no means as rare as was once believed. We have pointed out that in many members of these families the only manifestation of the disease is a high level of serum cholesterol. In several instances, such individuals have subsequently sustained cardiac infarction while under observation.

In some xanthoma families, relatively young persons may be found who exhibit arcus senilis in association with elevated serum cholesterol. Klatskin[2] reported two such young members in one family and we have made similar observations.[3] We have also found young adults with coronary atherosclerosis who are not members of a xanthoma family, but who, nonetheless, present arcus senilis and elevated serum cholesterol. The not infrequent appearance in the same individual of these three pathologic states, arcus senilis, coronary atherosclerosis, and elevated serum cholesterol, suggests that they are more than coincidental.

A clinical correlation between arteriosclerosis and altered cholesterol metabolism has been attempted by several investigators. The first reliable investigation was that of Mjassnikow[4] who, in 1925, showed that among sixteen patients with atherosclerosis, twelve of whom had angina pectoris, the serum cholesterol level was elevated in every one. Later, Andes and associates[5] found no difference between the cholesterol values of arteriosclerotic patients and normal individuals. However, it is clear that they were not dealing with atherosclerosis, since their criteria were based on palpation of the radial arteries and on evaluation of the condition of the dorsalis pedis vessels. The pathologic process involving these muscular arteries of the extremities is a medial sclerosis and not an intimal atheromatosis. Elliot and Nuzum[6] investigated blood cholesterol values in patients with hypertension and arteriosclerosis and found no correlation between

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the level of this blood lipid and the disorders studied. Their criteria also failed to differentiate between types of arteriosclerosis. Soon thereafter, Davis and co-workers[7] reported that among fifty-nine patients with proved angina pectoris the levels of cholesterol, total and free, lipid phosphorus, and fatty acids were higher than in a comparable group of control subjects. The ages of their patients ranged from 38 to 69 years. More recently, Steiner and Domanski[8] selected fifteen patients with proved coronary atherosclerosis whose ages ranged from 42 to 72 years and studied their blood cholesterol levels at varying intervals for as long as two years. This carefully conducted research revealed that the patients with coronary artery disease had much higher average serum cholesterol levels than similarly aged normal persons studied over the same period. They found an average serum cholesterol of 355 mg. per 100 c.c. in the group with coronary atherosclerosis and an average of 255 mg. per 100 c.c. in the control group. They also pointed out that, among patients with coronary artery disease, fluctuations in serum cholesterol levels from month to month were much greater than in normal persons, who maintain a relatively constant level through the years. This observation is of special importance and should be kept in mind when interpreting the significance of a "high normal" or "slightly elevated" cholesterol value in a patient with coronary atherosclerosis. Herrmann[9] found a mean serum cholesterol of 254 mg. per 100 c.c. among 120 patients diagnosed as having atheromatous heart disease with coronary thrombosis, mitral insufficiency, or angina pectoris. In a control group of fifty individuals, the mean serum cholesterol was 193 mg. per 100 cubic centimeters. Lerman and White[10] studied twenty-eight young patients with coronary artery disease and found that twenty-two of them had serum cholesterol values above 250 mg. per 100 cubic centimeters.

Most of these investigators did not confine their observations to younger individuals, nor did any of them study the incidence of hypercholesterolemia among the members of the patients' families. Since altered cholesterol metabolism seems to be the underlying disturbance predisposing to coronary artery disease in young members of families in which there are multiple cases of xanthomatosis, we thought it profitable to study the serum cholesterol levels and search for those stigmata that occur frequently in the presence of hypercholesterolemia in a group of relatively young patients with uncomplicated coronary atherosclerosis and in their siblings. It might be that xanthoma families represent only the extremes of disturbed cholesterol metabolism and that many patients with apparently uncomplicated coronary artery disease might fall into a similar pattern. If this were true, it might help to explain the familial occurrence of coronary artery disease and also give added significance to disturbed cholesterol metabolism in the etiology of coronary atherosclerosis.

If hypercholesterolemia occurs with some frequency in families, one or more of whose members have coronary atherosclerosis, it would seem probable that in these families a disturbance of cholesterol metabolism is the basic hereditary disorder predisposing to atherosclerosis.

METHODS AND MATERIAL

The patients were seen in the office practice of one of us (E.P.B.) and consisted of unselected, consecutive cardiac patients with proved coronary artery disease whose symptoms *began* under the age of 50 years. The vast majority were Jewish. Only patients with symptoms of coronary artery disease and electrocardiographic evidence of myocardial damage were included.

Over a period of one and one-half years, 122 patients were studied. These we have designated as primary patients. Each was examined for the presence of arcus senilis, xanthelasma, and xanthoma; and one or more serum cholesterol determinations were made by the method of Bloor.[11] There were 108 men and 14 women. Most were between 35 and 50 years of age, the youngest being 27 years and the oldest, 64 years. The average age was 45 years, the average age at onset of symptoms, 42 years. Those patients older than 50 years at the time of this investigation had developed angina pectoris prior to the age of 50 years.

We were able to study and evaluate the families of fifty of the 122 patients. By family is meant all or most of the siblings. In each of three families of six to seven siblings, we were able to study only three members. Salient features of the siblings' medical history, such as heart disease, hypertension, and diabetes mellitus, were recorded. The presence or absence of arcus senilis, xanthelasma, and xanthoma were noted and serum cholesterol determined. In a few instances, the parents and children of primary patients were studied also. It is germane to note at this point that in conducting this type of family study much difficulty will be encountered in obtaining complete or nearly complete families. Many of the patients do not know the whereabouts or health status of their siblings, especially of those living outside the United States. In the present study, additional limitations were created since many siblings were serving in the Armed Forces and were unavailable for investigation.

The range of normal serum cholesterol, according to Bloor's[11] method, is between 180 and 220 mg. per 100 cubic centimeters. By other methods,[12] 250 mg. per 100 c.c. is considered the upper limit of normal. For purposes of our study, however, a serum cholesterol level of at least 300 mg. per 100 c.c. was chosen as indicative of hypercholesterolemia, thus eliminating the influence of minor elevations of serum cholesterol.

RESULTS

A total of 307 serum cholesterol determinations were made. The values among the primary patients ranged from 199 mg. per 100 c.c. to 845 mg. per 100 c.c., the mean being 316 mg. per 100 c.c. (± 7.49 S.D.$_m$). The mean serum cholesterol in this series is somewhat lower than that reported by Steiner and Domanski[8] who found an average of 355 mg. per 100 c.c. in their small group of patients with proved coronary artery disease studied over a long period, but higher than that reported by Herrmann.[9]

Among the 122 patients, there were seventy-one (58%) whose serum cholesterol was elevated above 300 mg. per 100 c.c. (Fig. 1). The average serum cholesterol among these seventy-one patients was 365 mg. per 100 cubic centimeters. The average serum cholesterol among the remaining fifty-one patients was

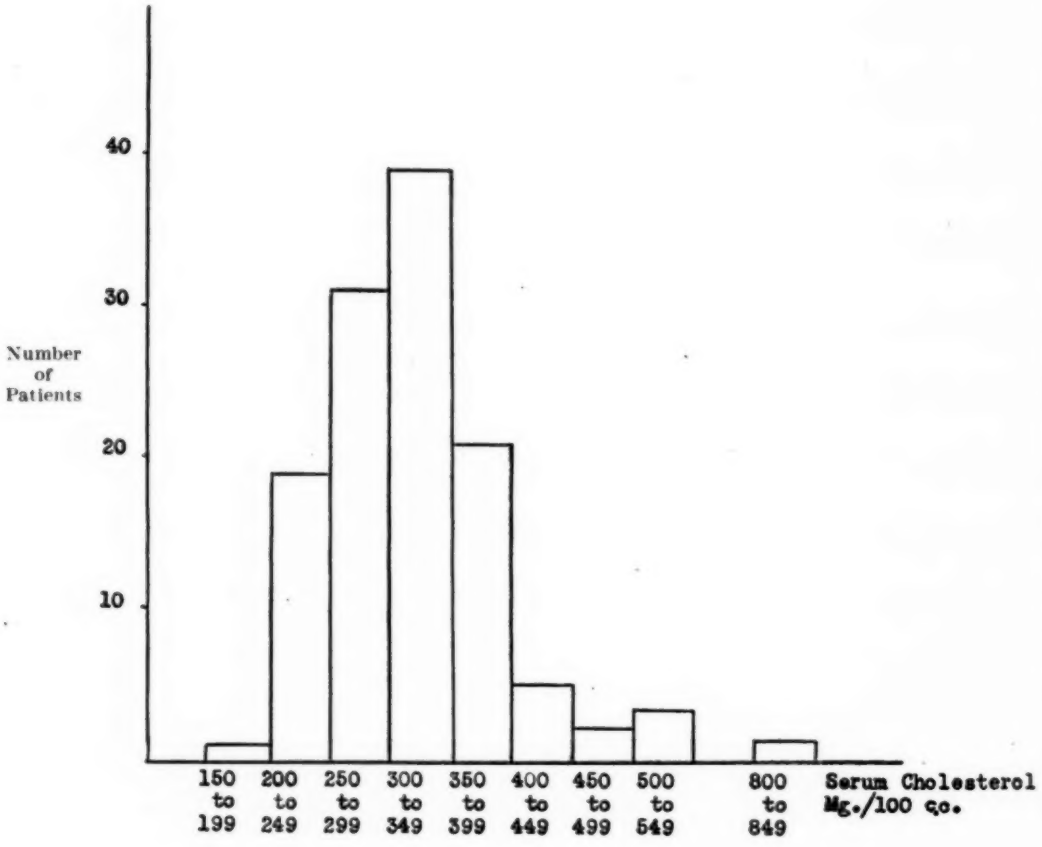

Fig. 1.—Distribution of serum cholesterol values among one hundred twenty-two patients with proved coronary atherosclerosis.

250 mg. per 100 cubic centimeters. There were twenty-two patients with arcus senilis, twelve with xanthelasma, and three with xanthomatosis. Comparing similar age groups, the incidence of arcus senilis in the presence of coronary artery disease was approximately the same in this series as in a previously reported study.[3] Among the twenty-two patients with arcus senilis and coronary atherosclerosis, seventeen had elevated serum cholesterol; among the twelve patients with xanthelasma and atherosclerosis, nine had elevated serum cholesterol; while among the three with xanthomatosis and coronary atherosclerosis, all had hypercholesterolemia.

Hypertension was present in twenty-one of the 122 patients, diabetes mellitus in three, and rheumatic heart disease in two. Hypertension was found in eight of the fourteen women of the group.

Of the fifty families studied, there were fifteen (30%) in which all or most of the siblings showed an elevation of serum cholesterol. (These are the first fifteen families listed in Table I.) There were nine families in which one-half of the members available for study exhibited hypercholesterolemia, while the other half had normal cholesterol values as judged by our previously mentioned standard. In twenty-six families, there was no general tendency toward elevated serum cholesterol, even though an occasional sibling exhibited hypercholesterolemia. In a few instances the primary patient was found to have normal serum cholesterol, but the siblings had hypercholesterolemia or stigmata of disturbed lipid metabolism.

Among the fifty families, several are of special interest:

CASE 10.—H. B. P., a man 52 years of age developed angina pectoris at the age of 47 years. He exhibited arcus senilis; his serum cholesterol was 322 mg. per 100 cubic centimeters. His mother had died at 58 years of age of "heart trouble" and diabetes mellitus; three sisters had died, one at 66 years of "heart disease" and two of "strokes" at 38 and 52 years, respectively. There were two living sisters whose serum cholesterol values were elevated to 350 and 325 mg. per 100 cubic centimeters. The patient's son had a normal cholesterol.

CASE 4.—C. W., a 37-year-old man, had a cardiac infarction at the age of 37 years. His serum cholesterol was 285 mg. per 100 cubic centimeters. However, a brother who suffered a cardiac infarction at 38 years of age had a serum cholesterol of 339 mg. per 100 cubic centimeters. Two other siblings had serum cholesterol values of 322 mg. per 100 cubic centimeters.

CASE 1.—F. Z., a woman known to have hypertension, 48 years of age, had a cardiac infarction. Her serum cholesterol was 345 mg. per 100 cubic centimeters. Her mother and one sister had died of "heart attacks." Hypercholesterolemia was present in three of four living siblings, being 330, 320, and 304 mg. per 100 cubic centimeters. The fourth sibling had a serum cholesterol of 240 mg. per 100 cubic centimters.

CASE 3.—I. F., a 48-year-old man, had a cardiac infarction. His serum cholesterol was 500 mg. per 100 cubic centimeters. There were two siblings, both of whom had hypercholesterolemia, the values being 435 mg. per 100 c.c. in a sister aged 46 years and 308 mg. per 100 c.c. in a brother aged 56 years.

CASE 8.—M. K., a man aged 43 years, had a cardiac infarction at the age of 41 years. His serum cholesterol was 327 mg. per 100 cubic centimeters. A brother had a cardiac infarction at the age of 32 years. His serum cholesterol was 318 mg. per 100 cubic centimeters. There were two sisters, aged 43 and 37 years, whose serum cholesterols were 320 and 263 mg. per 100 c.c., respectively.

CASE 11.—A 51-year-old woman had developed angina pectoris at the age of 49 years. There was xanthelasma of both upper lids. Her serum cholesterol was 362 mg. per 100 cubic centimeters. An only sibling, a sister aged 58, had xanthelasma since the age of 36 years. Her serum cholesterol was also 362 mg. per 100 cubic centimeters. A daughter, 28 years of age whom we were unable to examine was stated to be developing xanthelasma also.

CASE 37.—B. R., a woman 34 years of age, had had hypertension and coronary sclerosis for three years. Her serum cholesterol was 336 mg. per 100 cubic centimeters. Her father had died of cardiac infarction and her mother had angina pectoris. There were four siblings, one of whom,

TABLE I. SERUM CHOLESTEROL LEVELS AMONG SIBLINGS OF PATIENTS WITH CORONARY ATHEROSCLEROSIS*

NO.	PATIENT	SERUM CHOLESTEROL MG./100 C.C.	SERUM CHOLESTEROL OF SIBLINGS MG./100 C.C.						REMARKS
			SIBLING 1	SIBLING 2	SIBLING 3	SIBLING 4	SIBLING 5	SIBLING 6	
1	F. Z.	345	330	320	304	240			Sibling 5, woman, died age 46 of "heart attack." Mother died age 76 "heart attack"
9	L. K.	318	318	310	287				Sibling 3, woman 50 years of age, hypertension
4	C. W.	285	339	322	319	?†			Sibling 2, man, hypertension
8	M. K.	327	318	320	263	?	?		Sibling 1, man, cardiac infarction, age 32
2	S. K.	335	350	212					Sibling 1, man 51 years of age, hypertension. Mother died age 72, hemiplegia
3	I. F.	500	435	308					
14	S. D. R.	374	303	235					
5	C. J.	315	325	330	?				
7	L. P.	300	328	241	?				Sibling 2, man, hypertension and auricular fibrillation
13	M. T. S.	336	424	308	?	?	?		
10	H. B. P.	322	350	325	?	?	?	?	Sibling 3, woman, died age 38, "stroke"; sibling 4, woman, died age 52, "stroke"; sibling 5, woman, age 66, died "heart disease"; mother died age 58, diabetes and "heart trouble"
11	I. S.	362	362						
15	J. N.	358	408						
6	H. R.	390	370	?					Mother died age 52, diabetes mellitus; father died, 62, "heart attack"
12	B. S.‡	518	?						Four children; cholesterol values of 368, 326, 311, and 246
24	A. R.	330	296	?					Sibling 2, man, died cardiac infarction, age 41. Mother and father died of "heart disease"
27	A. C. K.	282	325						Father, age 70, has coronary artery disease
44	J. B. B.	230	300						
45	P. M.	277	366						Sibling, woman 59 years of age, has hypertension and coronary artery disease
46	C. R.	340	330	280	274				
47	M. S. L.	342	240						
48	A. S.	314	232						Father died age 58, cardiac infarction
49	J. W.	265	343						
50	J. B.	330	268						Father died age 57, cardiac infarction

40	E. R.	357	350	292	283	260	246	?	Sibling 1, man 50 years of age, has coronary sclerosis
25	P. K.	263	270	248	261	?	?	?	
18	I. T. K.	220	325	284	257	232	220		
21	J. W. W.	425	306	274	257	168	140		
28	H. A.	272, 238	357	262	241	220	220		Sibling 1, man aged 38, has arcus senilis
31	I. R.	311	196	178	168	?	?		Father, aged 60, died coronary artery disease
34	I. G.	199	256	246	224	?	?		Sibling 1, woman, aged 48, hypertension and angina pectoris; sibling 2, man aged 46, hypertension; sibling 3, man aged 54, angina pectoris
23	A. B.	351	300	286	?	?	?		
37	B. R.	336	357	241	227	207			Sibling 1, man aged 40 years, has marked arcus senilis; father died 58, cardiac infarction; mother has angina pectoris
16	H. N.	284, 256	278	263	187	?			
20	J. P.	350	277	210	206	?			
41	S. D.	333, 355	245	214	198	?			All siblings have hypertension
29	S. K. B.	236	270	217	?	?			
17	M. R. S.	332	293	260	255				
22	A. H.	289	320	276	246				
30	O. S.	232	278	263	184				
43	J. H.	224	238	212	165				
26	H. K. M.	260	270	244	?				
32	J. L.	215	182	167					Mother, age 53, hypertension and angina pectoris
33	G. S. S.	360	292	261					Father died age 46, arteriosclerosis. Sibling 1, woman, hypertension and arteriosclerosis
36	I. K.	225	216	208					Sibling 2, man, died cardiac infarction at 58. Both parents died of hypertensive arteriosclerotic heart disease
39	B. G.	330, 330	241	202					Mother has coronary artery disease, father has hypertension
19	N. M.	220	200						Sibling, man, cardiac infarction, age 40
35	H. S. B.	287	297						Sibling, man, had cardiac infarction, age 49
38	S. P. P.	254	207						
42	M. C.	269	264						Father, age 67, has coronary sclerosis and cholesterol of 232

*The first fifteen families listed are those in which hypercholesterolemia was present in all or most siblings. The next nine families listed are those in which one-half the members exhibited hypercholesterolemia and one-half had normal serum cholesterol. The remaining twenty-six families are those in which there was no general tendency to hypercholesterolemia, although an occasional sibling exhibited hypercholesterolemia.

† ? indicates sibling unavailable for study.

‡Since there were no living siblings, the children were studied

a 40-year-old man, had arcus senilis and a serum cholesterol of 357 mg. per 100 cubic centimeters. The other siblings had normal serum cholesterol values.

CASE 12.—B. S., a 56-year-old woman, who had diabetes mellitus, hypertension, and angina pectoris for many years, suffered a cardiac infarction. She exhibited xanthelasma. Her serum cholesterol was 518 mg. per 100 cubic centimeters. Her husband was stated to have xanthelasma also. Three of their four children had hypercholesterolemia, the values being 311, 326, and 368 mg. per 100 cubic centimeters. Two of them exhibited xanthelasma. The serum cholesterol of the fourth child was 246 mg. per 100 cubic centimeters.

CASE 24.—A. R., a man 36 years of age, had a cardiac infarction at the age of 34 years and again at the age of 36 years. His serum cholesterol was 330 mg. per 100 cubic centimeters. His mother and father had both died of "heart attacks"; his brother had died of cardiac infarction at the age of 41 years. The serum cholesterol of a living sister, 45 years of age, was 296 mg. per 100 cubic centimeters.

CASE 28.—H. A., a man 40 years of age, had a cardiac infarction. He exhibited marked arcus senilis and a serum cholesterol of 272 mg. per 100 cubic centimeters. His father had heart disease. There were five siblings, one of whom, aged 38 years, had arcus senilis and a serum cholesterol of 357 mg. per 100 cubic centimeters. Serum cholesterol values were normal among the remaining siblings.

CASE 41.—S. D., a 47-year-old man, had a cardiac infarction. He exhibited marked arcus senilis. His serum cholesterol values were 333 and 350 mg. per 100 cubic centimeters. Although the serum cholesterol value was normal in all four siblings, one of them, aged 42 years, exhibited marked arcus senilis.

The following case illustrates the gradual evolution of several manifestations of hypercholesterolemia in a young man:

CASE 48.—A. S., a 31-year-old man, was first seen in 1937 at the age of 24 years, three months after his father, aged 58, had died under observation of a coronary artery occlusion. In 1932, he had had "nervous indigestion," and in 1934, symptoms of peptic ulcer although gastrointestinal x-ray studies were normal. About three months prior to his first examination, while taking nitrous oxide for a tooth extraction, he experienced severe precordial pain with every heart beat, but had no residual pain or symptoms after the extraction. Two months later, a tooth was extracted under novocain anesthesia and he fainted three hours after the extraction. Subsequently he felt very tense and nervous for a number of days. When first seen, physical examination was completely negative; the blood pressure was 130/90. The electrocardiogram showed a flat T wave in Lead I and negative T waves in Leads II and III. He had no significant cardiac symptoms subsequently, but developed a severe psychoneurosis for which he received psychiatric treatment. A year later, his only cardiac symptoms were palpitation and occasional stabbing precordial pain. At this time the T wave in Lead II was flat, and the T wave in Lead III still negative. He had no significant symptoms until four years later, when he had a number of attacks of precordial pain radiating down the left arm. There was no change in the physical or electrocardiographic findings. For the first time, small xanthelasmas were observed at the inner canthi of both eyes. He was not seen again until the age of 31 years, when he complained of sharp left parasternal pain and a sense of suffocation on walking rapidly and with excitement. There was no change in the physical examination or in the electrocardiogram. There were large xanthelasmas of both upper eyelids and a beginning arcus senilis. The serum cholesterol at this time was 350 mg. per 100 c.c. and the cholesterol esters, 250. His brother, aged 29 years, was apparently well and had a serum cholesterol of 232 mg. per 100 cubic centimeters.

DISCUSSION

The role of cholesterol in the production of atherosclerosis has been a matter of contention since 1911, when Anitschkow[13] produced lesions resembling human

atherosclerosis in rabbits by feeding them cholesterol dissolved in oil. Subsequently, Leary[14,15] and many others confirmed these experiments, some of which were extended to include certain omnivorous,[16,17] as well as herbivorous, animals. Similar lesions have been produced lately in dogs by modifying the activity of the thyroid gland during cholesterol feeding.[18] Accompanying the atherosclerosis incident to feeding experimental animals large amounts of cholesterol, there appears a marked hypercholesterolemia. Because cholesterol feeding in man does not result in hypercholesterolemia, the significance of animal experiment has been questioned. However, feeding small amounts of cholesterol to rabbits over long periods will produce atheroma even though there is no elevation of serum cholesterol.[15] Since absolute elevation of serum cholesterol is not a prerequisite for experimental induction of atherosclerosis, other factors have been implicated, such as the rate of transport of cholesterol after its alimentary absorption or inefficiency of cholesterol metabolism itself. An extreme point of view is taken by Thannhauser[19] who believes that even primary essential xanthomatosis is not caused by a disorder of intermediary cholesterol metabolism, but that the metabolic disturbance of cholesterol lies within the reticular cells themselves. He states that hypercholesterolemia in itself does not cause the syndrome because xanthomas may develop while blood cholesterol is normal and cites as support the existence of a normocholesterolemic form of xanthomatosis. He believes that the development of atherosclerosis in patients with diabetic hyperlipemia is similar in pathogenesis to that produced in hypercholesterolemic rabbits, and contrasts it with the intrinsic formation of foam cells in xanthomatous tissue in primary essential xanthomatosis. He denies that pathologic hyperlipemia can be concerned in the development of atherosclerosis or atheromatosis in general. Against these conclusions may be posed the known fact that, in many different forms of lipoidoses and xanthomatoses, atherosclerosis is encountered almost exclusively in those associated with hypercholesterolemia, that is, in xanthelasma, xanthoma tuberosum and planum, tendon xanthoma, and in xanthomatous biliary cirrhosis. These are all associated with hypercholesterolemia at some stage of their development. Atheromatosis occurs early and extensively in diabetics with hyperlipemia and hypercholesterolemia; it occurs frequently in children with hypercholesterolemia due to nephrosis; it occurs in patients with myxedema in whom blood cholesterol is elevated. Pathologic studies by Ashoff[20] and Leary[21] revealed foam cells indistinguishable from xanthoma cells in early atherosclerotic lesions. For a comprehensive discussion of the problem of the pathogenesis of atherosclerosis and extensive bibliographies, the reviews by Hueper[22] and Katz and Dauber[23] should be consulted.

Regardless of the modus operandi, the clinical association of elevated serum cholesterol and atherosclerosis of the coronary arteries revealed by previous studies[4,7-9] and the present one would appear to be more than accidental. The occurrence of arcus senilis in young people with coronary artery disease should probably be regarded in the same light too, and not as a sign of premature senescence.

The occurrence of elevated serum cholesterol in one-third of the families of patients with coronary atherosclerosis suggests that among the hereditary factors that predispose to arteriosclerotic heart disease, a disturbance of lipid metabolism may play as significant a part as either hypertension or an inherited peculiarity of the coronary artery intima.[24] A priori, one would not expect an hereditary abnormality to occur in all or most members of every family. The variations in the familial incidence of coronary atherosclerosis may be accounted for by the degree of dilution or concentration of the tendency to abnormal cholesterol metabolism. If only one marriage partner has hypercholesterolemia, the tendency to this disorder will be diluted and fewer children will be affected; if both have hypercholesterolemia, the tendency will be intensified.[1] Thus the scattered instances of hypercholesterolemia in our material may have more significance than appears on the surface. Quite similar trends are observed in the hereditary distribution of diabetes mellitus.

The burden of a disturbed cholesterol metabolism may possibly be eased by dietary adjustment (low fat—low cholesterol diet), lecithin feeding, or other techniques such as the administration of thyroid substance and other compounds. By feeding lecithin to patients with hereditary xanthomatosis, depression of serum cholesterol may be obtained, especially when a cholesterol-poor diet is taken concomitantly.[25] This approach is promising and deserves further study.

The role of the thyroid hormone in the pathogenesis of atherosclerosis has been carefully investigated and it is known that thyroid administered simultaneously with cholesterol will prevent experimental atheromatosis in rabbits.[26] Conversely, thyroidectomy enhances the ease with which hypercholesterolemia and atheroma may be induced by cholesterol feeding.[27] Recently thiouracil has been administered to modify the function of the thyroid gland of dogs fed cholesterol in oil. Lesions resembling human atherosclerosis and arteriosclerosis in distribution and morphologic characteristics followed the hypercholesterolemia thus produced.[18] Davis and associates[7] investigated the basal metabolic rates of their patients with angina pectoris and hypercholesterolemia, but did not find any significant depression of thyroid function. Among their patients with coronary atherosclerosis, the average basal metabolic rate was minus 8 per cent, while among a comparable group of normal individuals, the basal metabolic rate was minus 13 per cent. Lerman and White,[10] on the other hand, in a recent study found low basal metabolic rates in about one-half of their patients with coronary artery disease and hypercholesterolemia and believed that the administration of thyroid substance benefited them. Further investigations in this direction are warranted.

Mention should be made of potassium iodide and organic iodide which, like thyroid substance, prevent the development of experimental atheroma.[28] However, they do not prevent hypercholesterolemia from developing. Perhaps a resurrection of the study of iodine compounds in relation to the prevention of atherosclerosis is timely.

In any event, since hypercholesterolemia reflects a metabolic disturbance, effort might well be expended in modifying its influence on the vascular system much as one attempts to obviate the complications of diabetes mellitus by diet and insulin. A pharmacologic counterpart to insulin for the treatment of hypercholesterolemia is not beyond the realm of possibility. By vigorously pursuing the various avenues of approach opened by the previously mentioned experiments, it may be possible to modify eventually one of the substrates of atherosclerosis and thereby reduce the incidence of coronary artery disease and death from cardiac infarction.

SUMMARY

Serum cholesterol was found to be elevated over 300 mg. per 100 c.c. in seventy-one members (58 per cent) of a group of 122 patients with proved coronary atherosclerosis whose disease began under the age of 50 years. The average serum cholesterol for the entire group of 122 patients was 316 mg. per 100 c.c. (± 7.49 $S.D._m$). The average serum cholesterol for the seventy-one patients who exhibited hypercholesterolemia was 365 mg. per 100 c.c., and the average among the remaining fifty-one patients was 250 mg. per 100 cubic centimeters. Arcus senilis was exhibited by twenty-two, xanthelasma by twelve, and xanthomatosis by three of the group. The great majority with these stigmata had elevated serum cholesterol levels.

Hypercholesterolemia (serum cholesterol of 300 mg. per 100 c.c. or more) was found in all or most of the siblings of one-third of fifty families of patients with coronary atherosclerosis. In nine more families, one-half of the siblings exhibited hypercholesterolemia.

This study lends support to previous clinical investigations and indicates that a disturbance in cholesterol metabolism is probably concerned in the genesis of some instances of coronary atherosclerosis. It also suggests that altered cholesterol metabolism may be the common denominator in most patients who have coronary artery disease and arcus senilis, or coronary artery disease and xanthelasma.

One of the hereditary factors responsible for arteriosclerotic heart disease may reside in abnormal cholesterol metabolism. Since therapeutic measures for correcting this metabolic disturbance may reasonably be anticipated, further investigations paralleling the present one are desirable.

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PRIMARY VASCULAR TUMORS OF THE PERICARDIUM

A Report of Two Cases

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PRIMARY pericardial tumors are distinctly rare. Yater[1] and Monckeberg[2] noted that they are usually sarcoma or lipoma. Much of the literature of the pericardial tumors deals with the group of problematical serosal endotheliomas or mesotheliomas. We wish to limit our discussion to a study of the vascular tumors of the pericardium. We are omitting all other tumors, including the controversial mesothelial group. To simplify this presentation further, we wish to exclude such vascular tumors as occur in portions of the heart other than the pericardium. Chronic inflammation with pseudoglandular spaces or prominent vascular channels in granulation tissue or in organization of blood clot, such as occurs so often in auricular thrombi, do not apply to the two instances reported here.

PRESENTATION OF CASES

Case 1.—The first case is one of benign cavernous angioma noted as an incidental finding in a patient who died of peritonitis following an operation for adenocarcinoma of the cecum.

This tumor was 1.0 cm. in diameter and presented itself as a localized deep-red discoloration in the epicardium of the left ventricle in the sulcus between the latter and the left auricle. The mass on section measured 1.0 by 0.25 centimeters. It was soft and showed some fine septa. It is significant that this patient also showed an identical cavernous angioma in the liver and an incidental leiomyoma of the kidney capsule extending into the kidney.

Microscopically, the tumor, sharply demarcated from surrounding fat tissue, consisted of large, thin-walled cavernous spaces filled with blood clot. Some of the channels showed thrombi. No reaction was noted in the pericardium.

Discussion: Tumors of this type in the pericardium have been described by Lefas,[3] Timme,[4] and Bencini.[5] Bencini described two cases, but he classified one as a pseudoangioma. He also mentioned a case described by Pommer as a complex vascular tumor which was called an angiofibroleiomyoma. This is of interest because it implies an origin from an embryonal rest. Bencini also quoted a case of Von Hoch, called a venous angioma, which he found mentioned by

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Monckeberg.[2] The case of Redtenbacker[6] may represent a malignant metastasizing cavernous angioma of the pericardium. The gross description of the primary lesion of the pericardium and the metastasis to the lungs definitely suggests a cavernous structure. The absence of a microscopic description makes it difficult to rule out a proliferating endothelial component of the neoplasm.

Tumors of this cavernous type are found elsewhere in the heart. Schuster[7] presented a tumor 2.5 by 1.5 cm. in a papillary muscle. Train[8] described a cavernous angioma, which reached the size of a hazel nut, in the interventricular septum. Muir[9] referred to a tumor "of considerable size in the upper margin of the right ventricle." Rau[10] reported a collection of ten cavernous channels in the region of the fossa ovalis. The authors have encountered several varixlike lesions of this type in this location.

The cases of Timme and Bencini, like our own, were incidental findings. In the patient of Lefas, death occurred suddenly because of the rupture of one of the vascular channels with bleeding into the pericardial cavity and cardiac tamponade. Bleeding may occur slowly, with a more prolonged period of symptoms. The case of Redtenbacker was of this nature with a prolonged period of progressive decompensation and venous engorgement.

CASE 2.—The second case is that of a progressive invasive cellular angioendothelioma with hemorrhage. A very similar instance was reported by Scheidegger[11] and the case of Redtenbacker may well represent another example. The gross features of both these instances are remarkably identical with the case we are presenting. Because of the significant clinical features, the history of this case is given in detail.

D. De J., a 27-year-old athletic white man, noted vague weakness during strenuous tennis matches. On several recent occasions, he "could not catch his breath." Such an episode occurred on May 6, 1942, and that night he noted pain in the stomach. He then became nauseated and vomited. His family physician found an enlarged heart and consulted with Dr. Daniel Porte,* a cardiologist. Physicial examination at this time revealed no heart murmurs; a split sound at the apex; the aortic second sound louder than the pulmonic second sound; blood pressure, 108/76; and weight, 170½ pounds. The electrocardiogram was not unusual (Fig. 1,*A*). The heart was enlarged to the right and left on fluoroscopy. On July 14, 1942, he was admitted to the hospital complaining of constricting and choking sensations in the throat. He ran a septic temperature varying from 99° to 103° Fahrenheit. Electrocardiographic examination on July 18, 1942, showed inverted T waves in Leads I and II and a small R wave in Lead CF IV (Fig. 1,*B*). On July 24, 1942, engorged neck vessels, puffy face, prominent chest veins, distant heart sounds, and a blood pressure of 114/88 were noted. Roentgenographic examination showed moderate increase in the size of the cardiac area, the cardiac measurements being: medium right diameter, 6.5 cm.; medium left diameter, 3.0 cm.; and the width at the base of the chest, 34.0 centimeters. Diffuse clouding was seen in the cephalic half of the left lung field, with the most marked density located centrally. The remainder of the lung field was clear but the lung markings were exaggerated. On July 26, 1942, a cough productive of bright red sputum developed. Pulmonary infarction and pericardial effusion were suspected. On Aug. 3, 1942, a second roentgenograph showed no change in size or contour of the enlarged heart, approximately 75 per cent resolution of the area in the left upper lobe, and a trace of pleural fluid at the left base (Fig. 2). Both thoracentesis and pericardiocentesis were dry. Blood cultures were negative. The sedimentation rate was 9.0 mm.

*We are indebted to Dr. Porte for the clinical details of this case.

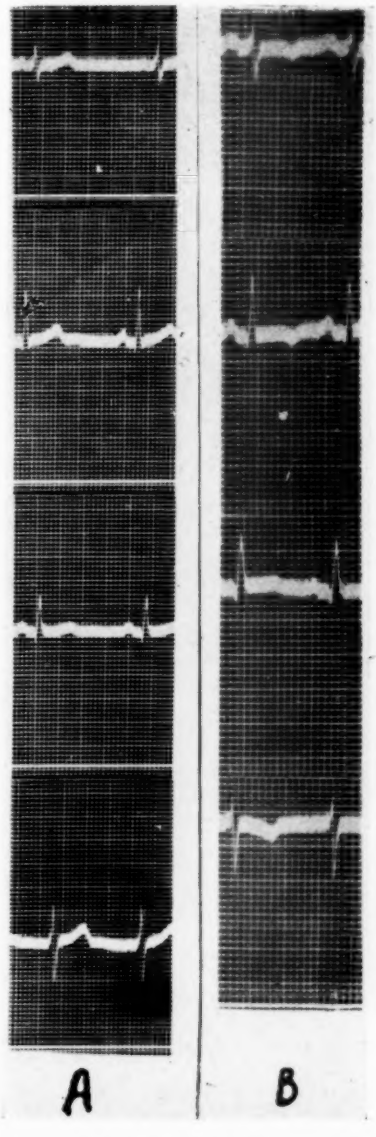

Fig. 1.—Electrocardiogram taken 130 days before death, marked *A* at left is not unusual; one made seventy-three days later, at right marked *B*, shows inverted T waves, Leads I and II, and small R wave in CF_4.

at the end of one hour. The blood count showed 3.57 million erythrocytes and 7,900 leucocytes per c.mm.; of the latter, 55 per cent were polymorphonuclear leucocytes and 45 per cent, lymphocytes. The hemoglobin content of the blood was 71 per cent.

He left the hospital Aug. 24, 1942. A downhill course followed and he expired Sept. 3, 1942.

Pathologic Findings: Autopsy revealed the pertinent pathologic findings to be limited to the heart. In addition, the deceased showed a moderate ascites, bilateral hydrothorax, marked

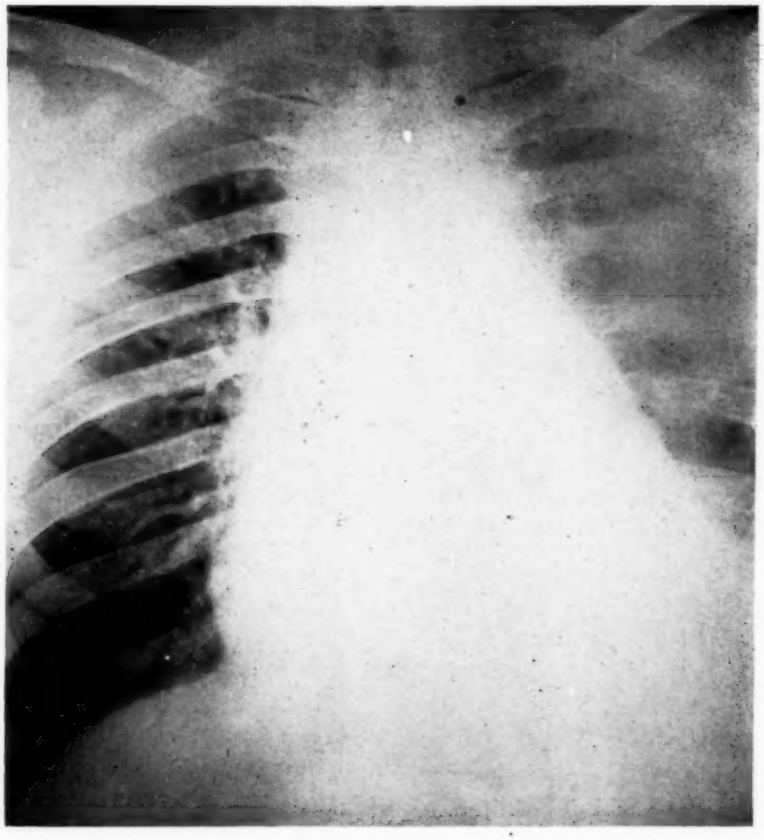

Fig. 2.—Roentgenogram made thirty-one days before death.

passive congestion of liver suggesting cardiac cirrhosis, multiple pulmonary infarcts, and a left axillary vein thrombus. No metastasis to other organs was found.

The heart, massively enlarged and adherent to the surrounding structures, measured 21 by 15 by 11 cm. (Fig. 3). The pericardial cavity was completely obliterated by thin, yet firm, adhesions. The parietal pericardium was stripped with difficulty from the visceral layer, but a distinct line of cleavage was maintained. It is significant that no free blood or organized clot was found within the obliterated potential cavity.

The variation in hue and consistency of the mass that thickened the epicardium and distorted the contour of the heart and its chambers was so marked as to make any attempt at localized description serve no useful purpose. Much of the distorting mass was frankly blood clot. In general, the large locules and cystic areas were found filled with such blood clot. Other areas showed rounded fibrin masses bearing a relationship to encircling paler trabeculae of fibrous or fibrin septae. In some zones, a spongy, porous character was noted in the tissue. In others, granular and hemogeneous inspissated fibrin material was suggested. In still other areas, a firm consistency and a friable pale granular tissue suggested compact cellular tumor islands. The latter zones were indefinitely demarcated and accounted for only a small portion of the distorted, discolored epicardial mass seen grossly.

When the parietal pericardium was stripped, the heart muscle was found encased in an encircling bloody, discolored, tumefied visceral pericardium. This hemorrhagic mass involved most

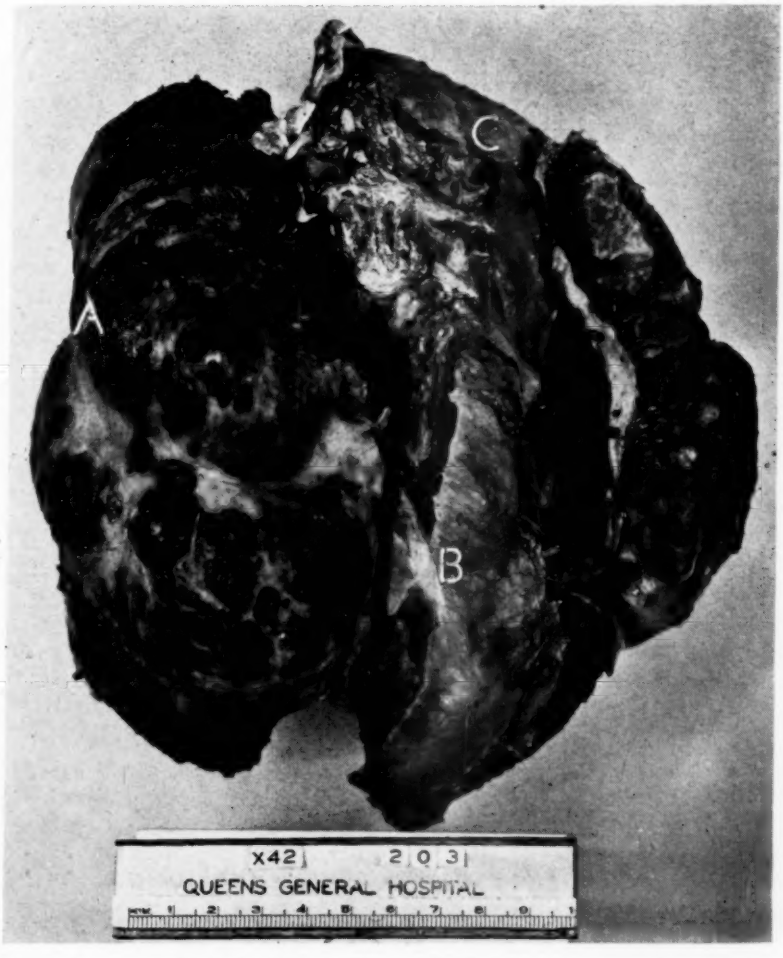

Fig. 3.—Posterior aspect of heart. *A* to *B*, auriculoventricular groove with transsection just to one side of the interventricular septum. Compression of superior vena cava by tumor at *C* with right auricle and inferior vena cava exposed below.

of the visceral serosal coat, penetrating here and there to the adherent parietal layer, particularly toward the apex. The heart itself was distorted, rounded, and globular in shape. The outlines of the heart chambers were sharply demarcated externally by depressed grooves (Fig. 3). The entire outer surface was red. A preserved visceral pericardial serosa could be made out except where the denuded surface had been torn in the separation of the parietal layer.

In general, the most marked distortion was found at the base. Here the hemorrhagic, tumor-like material encircled and distorted the entire posterior wall of the right auricle markedly, and of the left, to a lesser degree. It compressed and narrowed the mouths of the vena cava (Fig. 3,*C*) and the pulmonary veins, encircling the aorta and the pulmonary artery in the form of a thick layer on the posterior aspect (Fig. 4). These hemorrhagic zones merged with a similar area of involvement on the posterior aspect of the right and left ventricles. Anteriorly, the auriculoventricular groove on the right side was preserved and even exaggerated. Above the groove, the tumor thickening measured fully 5.0 cm. in the region of the auricles. Below the the groove, the distorted epicardium overlying the left ventricle measured 3.5 to 4 cm. (Fig.

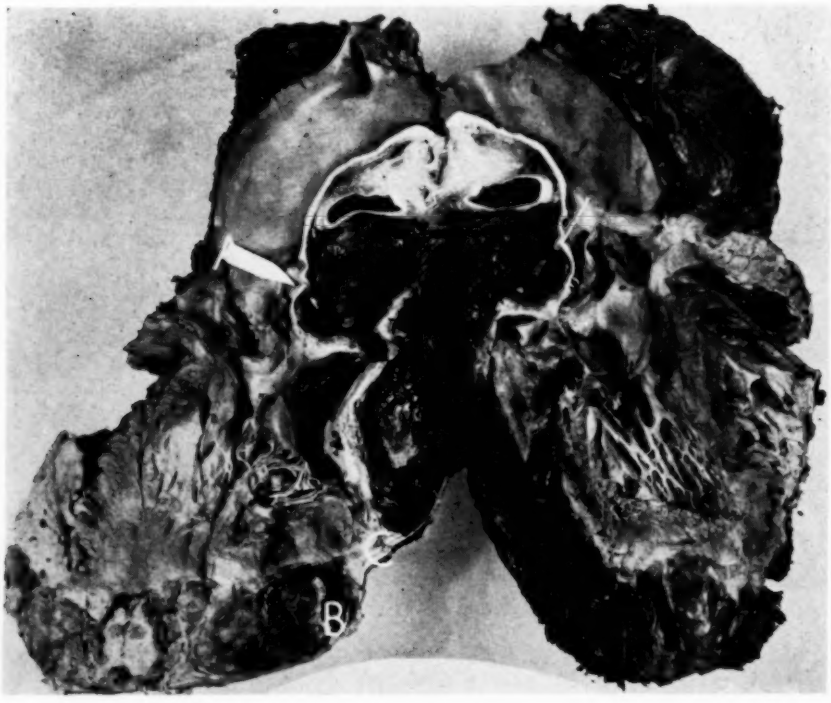

Fig. 4.—Posteroanterior section through the left ventricle and aorta, bisecting the right coronary ostium and cutting across the pulmonary artery. At *A*, the arrow points to the left half of the right coronary ostium. The probe is inserted into the right coronary artery. *B* shows the left ventricle and *C*, the auriculoventricular groove. The epicardium of the left auricle above is markedly involved.

4,*B*). The epicardium along the auriculoventricular groove proper measured only 0.5 cm. in thickness (Fig. 4,*C*).

The hemorrhagic material at the base of the heart extended to involve the base of the aorta where it was 3.0 to 5.0 cm. in thickness and was sharply delimited by the line of reflection of the parietal pericardium. The basilar involvement also completely encircled the pulmonary artery, beginning just above the level of the pulmonary valves. Here it measured 3.0 to 5.0 cm. in thickness. At this point, the tumor mass seemed to extend beyond the pericardial reflection to the parietal layer proper for a short distance.

In the region of the ventricles, the tumor was definitely thinner as compared to the auricular or basilar involvement (Fig. 4,*B*). The right ventricle was involved posteriorly and laterally where the tumor was quite thick again, measuring 4.0 to 5.0 cm. in some areas. The chamber of the right ventricle had its contour distorted by the inward bulging of the tumor. Anteriorly, the epicardium of the pulmonary conus adjacent to the right ventricle and the most proximal pulmonary artery was least involved. The epicardium here measured only 5.0 mm. in thickness (Fig. 4,*C*) and showed serous edema of the fat. The left ventricle showed marked distortion by the encircling reddish tumor mass (Fig. 4,*B*) except anteriorly, where again less distortion existed. This relatively uninvolved zone of left ventricular epicardium included the apex and basilar portion of the ventricle adjacent to the anteriorly placed uninvolved right ventricle and pulmonary conus already described.

The myocardium throughout showed no evidence of invasion by the tumor tissue grossly, but the heart wall seemed stiffened and less pliable. The muscle of the left ventricle measured

15 to 16 mm. in thickness. The chambers seemed small in proportion, especially those of the ventricles. The tumor at the base of the heart encircled and compressed the mouth of the right coronary artery (Fig. 4,*A*). The rest of the coronary arteries and the coronary sinus showed no alteration.

The appearance definitely indicated that the tumor was not in the pericardium but in the visceral layer, and limited to this zone except for relatively small areas of extension to the regional myocardium and the parietal pericardium. The stripped parietal pericardium was slightly thickened throughout, and presented sharply delimited areas of thickening which appeared as red protrusions. There were more than a dozen such protrusions, varying in size from 0.5 to 1.0 cm. in diameter. On section, they were found to be lobulated and porous and contained clotted blood. Other protuberant nodules were made up of firm, granular white tissue and suggested altered fibrin, compact cellular zones of vascularization, or solid zones of tumor tissue. The nodules could be separated from the parietal pericardium with difficulty through a cleavage plane corresponding to the original serosal layer of the pericardium, leaving rounded pitted depressions covered by adherent hemorrhagic material. Both visceral and parietal pericardium on their opposed surfaces showed a brownish staining produced by a fine granular film suggesting fibrin.

Microscopic Description: The microscopic sections taken throughout the mass were stained by hematoxylin and eosin, Mallory's phosphotungstic acid, and van Gieson and Mallory's connective tissue stains. In many sections only blood clot could be made out. Some of the clot showed mainly fibrin with hemolysis of the red cells and distinct lamellation. Other areas showed fresh nonlamellated clot. Much of the trabeculation referred to in the gross description represented septa of older fibrin contrasted with fresh red blood coagulum. Some of the septa were fibrous. Much of the blood clot was found within dilated cavernous channels lined by hypertrophic and hyperchromatic small-celled tumor tissue. In some areas, the fibrous septa were lined by a single layer of such cells. The living tumor tissue of the cavernous channels showed zones of heaped-up, proliferating, compact cellular tumor, which protruded as a nubbin into the enclosed blood clot. There was nowhere seen a true papillation with delimited papillary epithelial-like tissue. The papillary masses were revealed as heaped-up cellular areas of tumor tissue without any coherent histologic organization. Compact cellular zones of tumor tissue were seen in small foci and suggested the complete filling of previously existing cavernous channels, with little blood clot present.

The cytology of the tumor tissue was also variable. In the main, the tissue suggested a sarcoma. Only the nuclei were discernible in most of the tumor, with the cytoplasm indefinitely outlined, indeterminate, scant, and often suggesting a syncytium. The linear outline and shape of the nuclei varied markedly. Most of the chromatin was found in the nuclear membrane, which appeared as a uniformly sharp line. The remainder of the nuclei showed relatively small nucleoli and only small flecks of chromatin. This gave the nucleus a vesicular appearance, despite evident hyperchromatism. Some tumor cells were rounded, with limited borders and deep staining eosinophilic cytoplasm. No bizzare pleomorphism or atypical giant cells were found.

In some zones, smaller but definite tumor-lined vascular channels (Fig. 5) were filled with red blood cells or clot of a post-mortem character. Such areas merged with others where a distinct resemblance to granulation tissue was evident. Some of the capillary buds merged with solid columns of tumor cells, with the demonstrable central vacuolization suggesting an actual embryonic process of capillary channel formation. All of these zones of formative vascular channels merged with compact cellular diffuse tumor-cell areas.

In the region of the left ventricle, the tumor tissue was cellular and solid and invaded the underlying myocardium, in several sections, but only for short distances. The involved muscle showed atrophy. The living capillary endothelium between the muscle bundles showed progressive changes of transition to tumor tissue. In the regions of the left auricle, toward the apex, and on the masses found on the stripped parietal pericardium, the tumor showed a prominent cavernous structure with little tumor tissue, which was limited to the lining of such channels. The tumor overlying the right auricle showed outstanding cellularity. The cellular tissue here presented the most marked anaplasia, with irregularity in the contour and staining of the nuclei.

Fig. 5.—H & E microphotograph, x375, of tumor tissue in epicardium which demonstrates the tendency to form vascular spaces and solid masses of cellular tissue showing elongated vesicular nuclei with prominent nucleoli.

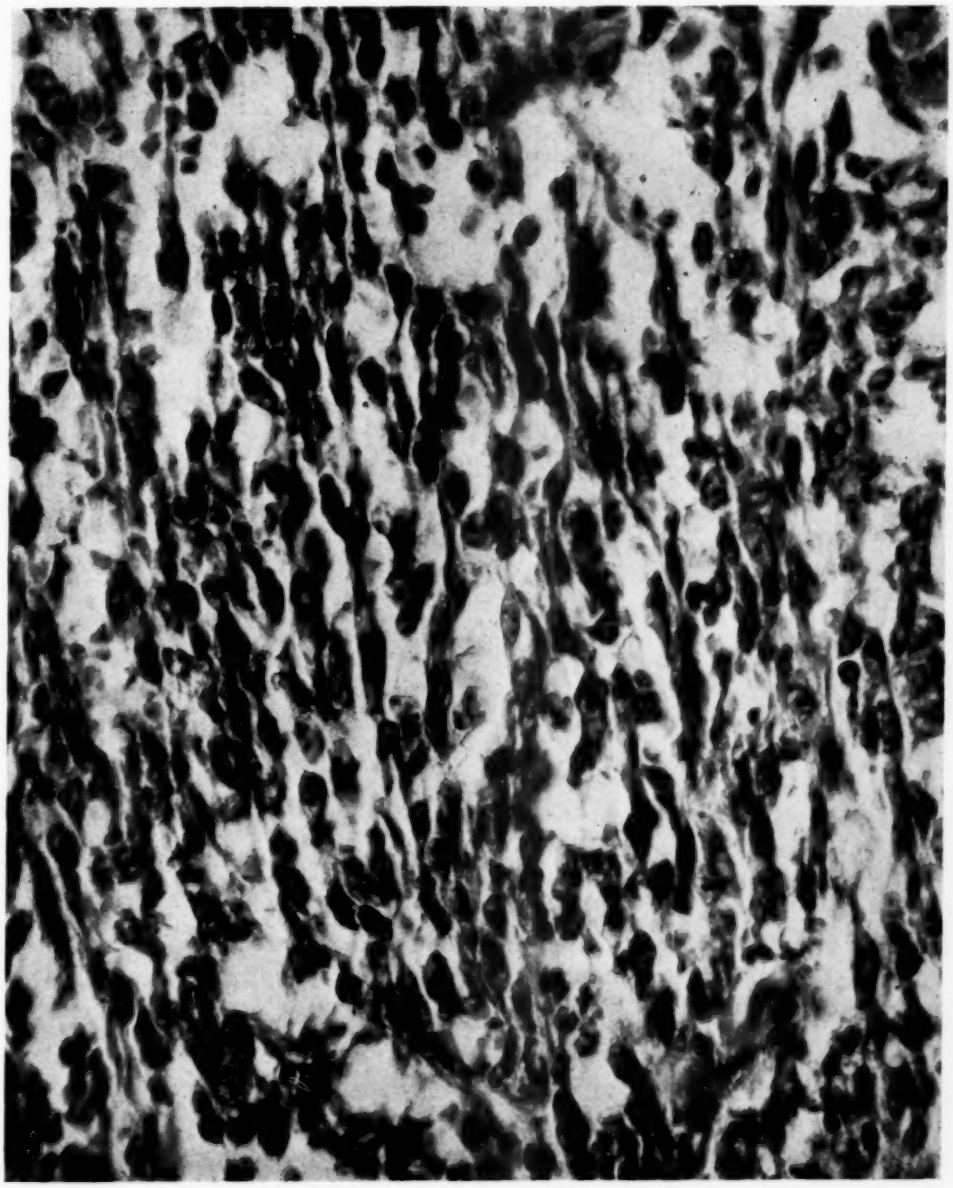

Fig. 6.—Higher power, x875, showing compact cellular areas of characteristic cells with distinct nuclear membranes and prominent small nucleoli and distinct, prominent vacuolization suggesting mechanism of channel formation.

No hematopoietic tissue was encountered in any of the capillary areas or larger lumina or in the more cellular zones.

The lungs showed an area of infarction undergoing resolution and organization. In the remaining lung tissue, there was some fibrosis with prominent heart failure cells and some vascular sclerosis. Adherent fibrin coated the pleura. The liver showed some edema and marked congestion but no true cirrhosis.

Discussion of Case 2: The case of Scheidegger[11] presented gross and microscopic features quite similar to this case. His tumor, however, metastasized to the mediastinal lymph nodes, the liver, the lung, and particularly to the pleura. One metastatic focus involved a pre-existing cavernoma of the liver. There is special significance to the localization of this metastasis. Such metastasis to cavernomas has been frequently found by us in many forms of malignancy. The case of Redtenbacker also showed metastasis to the lung, particularly the edges of the lower lobes. As noted, the inadequacy of the descriptive detail makes the exact classification of this tumor difficult. It is quite possible, in view of the metastasis present, that solid endothelial proliferative areas could have been seen on microscopic study. An endothelioma of the pericardium of serosal cell origin was described by Hines and Nolan.[12] Their description, however, noted vascular channels with blood content, and the possibility of a vascular endothelioma must be entertained.

DISCUSSION

Tumors of this structure have been described as occurring in other parts of the heart. Such angioendotheliomas or angiosarcomas have been noted most often as originating from the auricular wall, particularly from that of the right auricle. There exists an abundant literature dealing with the problem of differentiation of these tumors from true myxomas and vascularized organized thrombi. It is our own conviction that many reported cases of angioendotheliomas of the heart represent instances of vascularization of thrombi, rather than true neoplastic blood vessel proliferations or aggressive endothelial tumors. However, there are instances in the literature of metastatic foci which seem to confirm biologically the morphologic appearance of true malignant neoplasia for some of the reported cases.

Orsos[13] attempted a classification of the vascular tumors and described tumors of this type with very similar histologic features as gemmangiomas. None of his eleven cases involved a pericardial neoplasm.

From the standpoint of the origin of these tumors, the finding of coexisting angiomas elsewhere deserves consideration. The first case showed a cavernoma of the liver and a leiomyoma of the kidney. In the case of Scheidegger, several vascular cavernous angiomas were found in the liver. Redtenbacker described a papilliferous pigmented nevus of the skin on the shoulder. His description does not favor a vascular type of nevus. The thought is a compelling one that these tumors represent vascular anomalies or may originate from pre-existing

nevi or vascular rests. Such islands, or rests, in the pericardium may acquire progressive active growth features and metastasize much as the ordinary malignant skin angiomas are known to do. We do not mean to imply that the malignant angioendotheliomas originate from the cavernous structures. It is our impression, rather, that they represent two independent entities. The capillary nevi, in general, are known to become aggressive more often and probably originate from a nevus rest which has a capillary structure at the outset. Cavernous angiomas are considered hamartomas and rarely present metastasis or progressive growth in the ordinary sense. An occasional cavernoma will metastasize to lung or lymph nodes, as in the cases depicted by Ewing.[14] The case of Redtenbacker may well represent such a metastasizing malignant form of cavernous angioma originating in the pericardium.

Mahaim[15] considers this neoplasm, at least in its counterpart described by Scheidegger, as a "very vascular coelotheliome." His classification which grouped the malignant pericardial tumors under the general heading of "malignant coelotheliome," though quite satisfactory clinically, represents an oversimplification from the pathologic standpoint.

Yater attempted a delineation of a clinical picture for tumors of the pericardium. It would seem that the clinical picture can present such marked variations that the proposed isolation of a specific clinical entity is of doubtful assistance. The clinical course will depend upon the proportion of hemorrhage in the tumor mass and its rapidity of occurrence, as well as the presence or absence of an obliterated pericardial cavity. In some of the cavernous tumors a rapid tamponade causes sudden death, as in the case of Lefas. In the cases of Scheidegger and Redtenbacker, an increasing decompensation with vena caval compression was slowly progressive, with sufficient time for metastasis to occur. In the second case presented here the course was rapidly progressive and death occurred before metastasis had taken place. If a previously healthy individual shows, without known cause, a rapid evolution of the symptoms of decompensation and an enlarged cardiac shadow, a pericardial tumor should be considered.

CONCLUSION

1. A cavernous angioma of the pericardium and a case of a progressive malignant angioendothelioma of the pericardium have been presented.

2. The literature dealing with pericardial vascular tumors has been reviewed and only three definite cases of the cavernous form and two specific instances of malignant angioendotheliomas were found.

3. The possible origin of such tumors has been discussed.

4. The variation in the clinical course has been analyzed.

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SUDDEN AND UNEXPECTED NATURAL DEATH

II. Coronary Artery Sclerosis

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THIS is the second in a series of papers on sudden and unexpected natural death, verified at necropsy, in 2,030 consecutive cases in the Office of the Chief Medical Examiner, New York City, for the Borough of Manhattan. In the first paper,[1] a survey was made of the circumstances under which the Medical Examiner assumes jurisdiction, of the various pathologic conditions encountered, and of the sex, age, and racial distribution of the cases under consideration. That survey may be briefly summarized.

The 2,030 cases were observed during the period from Jan. 1, 1937, to June 30, 1943; death was unexpected in that the victims were apparently healthy at the time of death, and sudden because death took place usually within twenty-four hours after the onset of symptoms. The designation "natural death" indicates that death resulted exclusively from disease unassociated with external violence or poisoning.

The material was gathered from a community the population of which is made up of all races and includes relatively many adults. The Census Bureau records a total population, in 1940 in Manhattan, of almost 1,900,000, of which 51 per cent were women; the same sex distribution holds true for the 1,580,000 white persons. Among the 298,000 Negroes, women totaled over 55 per cent, but for the other races, largely Asiatic, there were but 2,186 (15.6 per cent) women compared with 11,748 men. The preponderance of adults in the population is striking; slightly more than three-fourths of all persons on Manhattan Island were over 21 years of age. When it is recalled that at any given time New York City normally has about 500,000 visitors, most of whom are adults, and that the majority of them spend their time in Manhattan, the reservoir from which material for this study was collected is overwhelmingly composed of mature individuals. Also, during the working day, many adults from the other four boroughs of the city and from suburban communities add to the fixed population of Manhattan.

Diseases of the heart and aorta were first among the causes of death (45 per cent), and were succeeded, in order, by diseases of the respiratory tract (23 per cent), nervous system (18 per cent), digestive organs (6.2 per cent), urinary tract (almost 2 per cent), and genital apparatus (1.3 per cent). A

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miscellaneous group accounted for 4.4 per cent of the deaths, of which three-fifths, during the period under discussion, represented estivo-autumnal malaria in drug addicts.

The role of coronary arteriosclerosis in this galaxy is best illustrated and emphasized by the fact that in almost one-third (30.4 per cent) of the entire series of 2,030 cases death was caused by that disease. There is much misunderstanding of the symptomatology and manner of death, in relation to the fatal lesions in this disease, which has been responsible for medicolegal confusion. Responsibility for the misunderstanding may be attributed in part to the lack of appropriate data from medicolegal authorities; a share in the culpability belongs to those clinicians who attempt to evaluate coronary artery disease, where there have been no premortem symptoms, on the basis of experience with the more common examples encountered in office and hospital practice. Pathologists are not without blame, for, like clinicians, they also have too readily analyzed their material with criteria gained from autopsies of patients dying after days or weeks in the hospital. It cannot be overemphasized that the problems confronting the medical examiner in sudden and unexpected natural death, of whatever cause, require standards of evaluation with which the clinician and hospital pathologist are not familiar. Any attempt by the latter to substitute their experience for that of the medical examiner may lead to erroneous conclusions, especially important when testimony is offered in both criminal and civil actions, and serve to confuse and mislead their legal confreres.

Before presenting the data on coronary artery sclerosis and the conclusions drawn from their study, it should be pointed out that the finding of a severe grade of sclerosis of the coronary arteries does not, per se, mean that such disease is the cause of death. Death should not be attributed to diseases of the coronary arteries without a complete study of the circumstances and a full autopsy, including examination of the brain, and, where necessary, chemical examination of organs. In the absence of significant changes in organs other than the heart, with chemical findings unrelated to the death, and with a review of the manner of death (not always available), death may be ascribed to coronary artery disease when such disease is present and in adequate degree. Failure to observe all these criteria will result only in mistaken diagnoses.

The only work now available on coronary artery disease as a cause of sudden and unexpected death in a comparable large urban civilian population is that of Hallermann,[2] whose monograph appeared in 1939. During a five-year-period (1931 to 1935) at the Berlin Institute for Legal and Social Medicine, there were 6,481 necropsies in the noncriminal ("aussergerichtlich") category. Omitting ninety-eight cases of syphilitic mesaortitis with coronary ostial obstruction and four of coronary embolism, there were 681 instances of coronary artery sclerosis, including its complications and sequelae; an incidence of 10.5 per cent of the entire material. This represents a superficially marked deviation from the 30.4 per cent (617 cases) in our total material of 2,030 autopsied cases. The discrepancy may be explained in part by several facts. First, Hallermann's cases were

gathered from all of Berlin, the population of which undoubtedly included relatively more persons under 21 years of age than does that of Manhattan. Second, more necropsies may have been performed in the noncoronary-disease age groups. Third, factors militating against the necropsy in American cities are, generally speaking, absent in Central European communities. The institution of the autopsy has been widely accepted abroad, and legal requirements facilitate greater ease in its performance; the advent of the Hitler regime during the period of Hallermann's study probably made popular objection to any action by the authorities, even in medicolegal matters, less articulate. Finally, since it is not so stated, the Berlin total of 6,481 autopsies probably included those conditions specifically left out of this study (alcoholism, drug addiction, and so forth).

The two studies do coincide, however, when deaths from coronary artery sclerosis are compared with those from all heart and vascular diseases. The New York figures are 617 of 912 cases, or 67.7 per cent, while those of Berlin[2] are 681 of 1,028, or 66.3 per cent.

Coronary artery disease as a cause of sudden death is almost exclusively a malady of white men; only 6 per cent (thirty-six cases) of the subjects were women and these were only of the white race. A single Asiatic and twenty-three Negroes (3.7 per cent) were found among the male subjects, thus making the white male contribution to coronary artery sclerosis slightly more than 90 per cent. There is a striking disparity between the 3.7 per cent of male Negro cases and the 14.5 per cent representing the proportion of the male population which they formed. The discrepancy remains great even if all of the visitors to Manhattan are considered as white, and as men, thus reducing the Negro male population to 9.4 per cent. Lest it be thought that there is a relative immunity of Negroes to sudden and unexpected death from cardiac disease, it may be pointed out that, of the forty-six cases of death attributed to obstruction of the coronary ostia in syphilitic aortitis, eighteen (39 per cent) or two and one-half times the expected percentage, were Negroes. Syphilitic aortitis, however, does not come within the scope of this paper.

Hallermann's report does not include racial analysis of his material; even before Hitler's advent to power, the Berlin population was composed almost exclusively of white persons. There is, however, a marked difference in the sex composition of the cases in the Berlin monograph and those reported here. In the former, almost one-fourth of the cases of coronary artery sclerosis are women, while the New York group has but 6 per cent. Unfortunately, Hallermann does not give any indication as to the distribution and composition of all cases of sudden and unexpected natural death, so that comparisons are difficult. The two cities do resemble each other in that those engaged in the more humble occupations contribute much of the material in the category under investigation.

How do the various age groups stand out in the apportionment of coronary artery disease? The following figures deal only with white men, who, as already stated, make up 90 per cent of the cases in this classification. Grouping is by half decades (Fig. 1), with no cases found in persons 19 years of age or under.

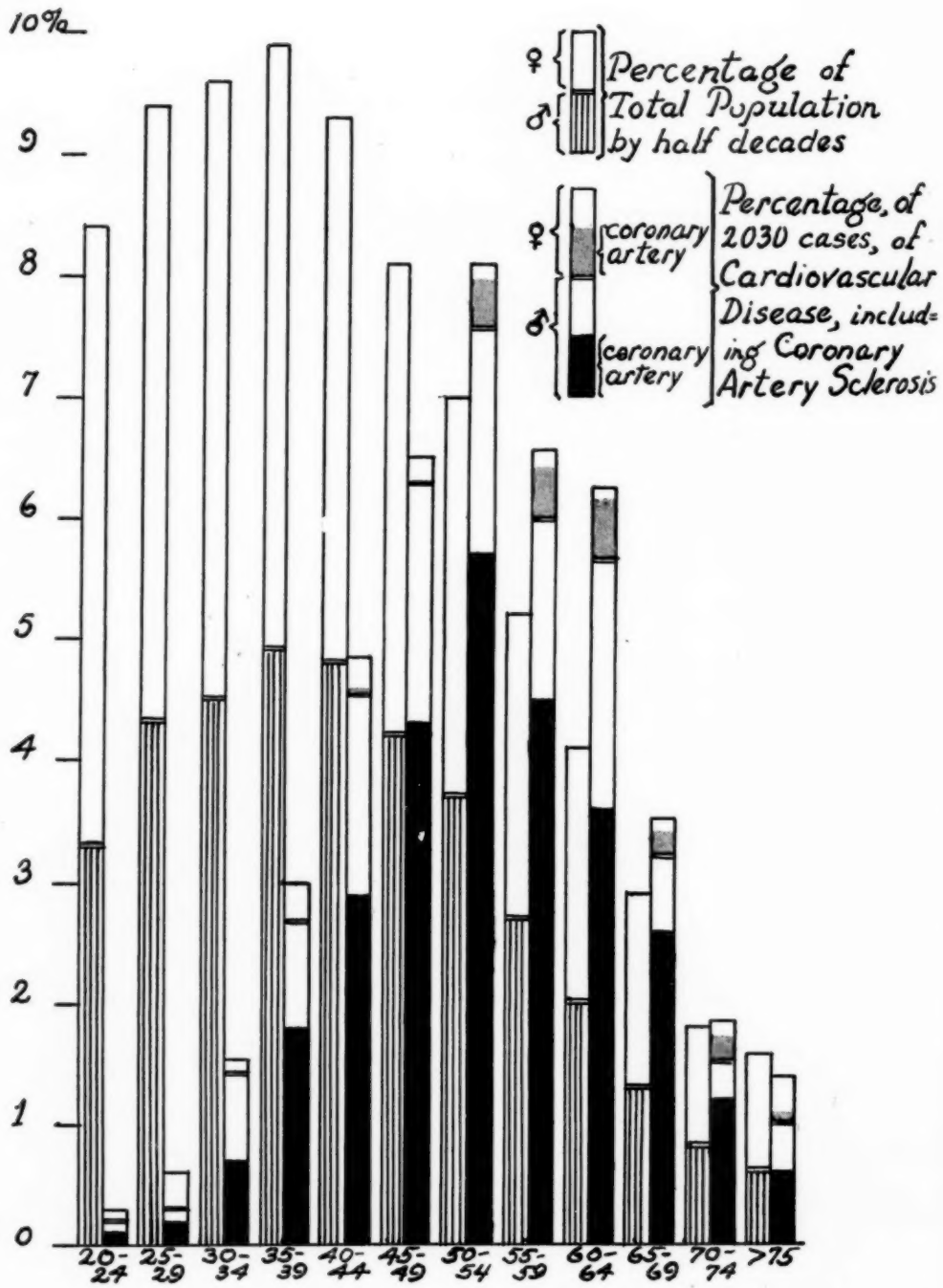

Fig. 1.—Graph showing percentage-age distribution, by half-decades, of (a) population of Borough of Manhattan, New York City, 1940, (b) cardiac and aortic disease among 2,030 cases of sudden and unexpected natural death (1937-1943), and (c) coronary artery sclerosis among the 2,030 cases.

As may be expected, the two half decades between 20 and 29 years provide but a fraction, 0.1 and 0.2 per cent, as compared with 3.3 and 4.3 per cent, the proportion of the white male population furnished by this age group. The next half decade, 30 to 34 years, still lags, but to a lesser degree; 0.7 per cent contrasted with its 4.5 per cent of male inhabitants. From 35 years of age onward, each group provides a greater contribution in proportion to its share of the population; thus, the age group 35 to 39 years provides 1.8 per cent as contrasted with 4.9 per cent of the population in this age range; 40 to 44 years provides 2.9 per cent, as compared with 4.8 per cent. From 45 years onward, each half decade contributes a greater percentage of sudden deaths than its share; 45 to 49 years provides 4.3 per cent as compared with 4.2 per cent of population; 50 to 54 years contributes 5.7 per cent compared with 3.7 per cent; 55 to 59 years, 4.5 per cent compared with 2.7 per cent; 60 to 64 years, 3.6 per cent compared with 2.0 per cent; 65 to 69 years, 2.6 per cent compared with 1.3 per cent population; 70 to 74 years, 1.2 per cent compared with 0.8 per cent; the group above 75 years contributes 0.6 per cent, equaling their percentage of the population. Thus, in this autopsied series, the incidence of coronary artery disease as a cause of sudden death in white men reaches a peak between 50 and 54 years and then gradually falls, its percentage remaining in excess of the percentage of the population that this age group furnishes. In summary, it can be stated that the thirty years between 44 and 74 have one and one-half times as many cases of sudden and unexpected death from coronary artery sclerosis and its complications and sequelae as would be expected from their contribution to the population.

It is difficult to compare Berlin with Manhattan Island in the age distribution of the cases. First, Hallermann's monograph does not include an age analysis of Berlin's population. Second, he does not give statistical data for all types of coronary artery sclerosis (thrombotic, nonthrombotic, with or without infarction, and so forth); he describes sclerosis, with or without old occlusion, and fibrosis of the myocardium for the period in question (1931 to 1935). As an appendix, Hallermann does give a brief summary of additional cases for 1936 to 1938. During these three years, the fourth to the sixth years under Nazi rule, there were about one-third more sudden and unexpected natural deaths from cardiovascular disease than during the preceding five years (two years under the Weimar Republic and three years under Hitler). The cases of coronary artery disease represented 66.3 per cent of cardiovascular deaths in the earlier, and almost the same proportion (62.5 per cent) in the later period, almost exactly corresponding to the New York values, as has already been noted. If a comparison is made of male deaths in New York with those in Berlin for the later period (1936 to 1938), there is a general trend toward higher values in the earlier age groups in New York; for example, 8.9 per cent as compared with 3.0 per cent in the fourth decade. The disparity sinks to 2:1 for the fifth decade, and practically disappears for the ages of 50 to 60 years. The two cities are virtually similar for the ages of 60 to 70 years, but for the next decade Berlin has twice the contribution of New York.

Of the 617 instances of coronary artery sclerosis, almost three-fourths (73.3 per cent) had no grossly demonstrable associated fresh thrombosis of the

vessels. This approximates the 95.3 and 80.2 per cent of the two Berlin periods. In most cases, atheromatosis with or without calcification had produced significant diminution of luminal caliber, so that, physiologically as well as anatomically, the effect was not different from that of old thrombosis. It should not be forgotten that functionally a narrowed sclerotic vessel, even without complete occlusion of the passage, may be inadequate in furnishing a satisfactory blood supply to the myocardium. From the statistical viewpoint, therefore, sudden unexpected natural death from coronary artery disease is best recorded simply as "coronary artery sclerosis."

Nonthrombotic sclerosis was free of fibrosis in 45 per cent and was associated with fibrosis in only 50 per cent, while infarction occurred in only 5 per cent. The Berlin statistics differ sharply from these values, since nonthrombotic sclerosis was associated with myocardial fibrosis in over 80 per cent of the cases, a difference in part attributable to the personal interpretation of the prosector as to what constitutes "fibrosis."

Slightly more than one-fourth of the instances of coronary artery sclerosis were complicated by fresh thrombosis. Seventy-five per cent (in the Berlin series, 60 per cent) of the cases with thrombosis showed infarction of the myocardium, both with and without antecedent fibrosis, in almost equal proportions.

In an attempt to obtain further clarification, more detailed information was obtained from the protocols of the cases studied during 1938 and 1939. Every profession and trade was represented, with the more humble callings expectedly predominating. In almost one-half of the cases (47 per cent) death took place in the street, or while at work, or in a public place; in an equally large proportion, the scene was the home or a hotel room. In the home, the bed (17 per cent) was as often the place of death as all other parts of the house combined (kitchen, bathroom, and so forth, 17 per cent). Those who died in hotels were generally found dead in bed, although not always following a night of rest and relaxation.

How much time elapses between onset of symptoms and death? Because a little more than one-third of the cases were found dead in bed, the time element is unknown in that large portion. Of the remaining slightly less than two-thirds, in which the period is known, almost 80 per cent died virtually instantly. Of the remainder, more lived beyond an hour than died in less than that time.

What relationship, if any, has the drinking of alcoholic liquors in the precipitation of death in coronary artery disease? In slightly less than 75 per cent of the autopsies, during the years under closer examination (1938 and 1939), alcohol determinations were done on liver or brain, chiefly the latter; four-fifths of these gave negative results. Of the remainder, 35 per cent gave results of 1 plus or a trace. It seems evident, then, that acute alcoholism plays no obvious role in the promotion of death in this disease.

It is sometimes asserted that coronary artery disability is associated with normal heart weight, and that cardiac enlargement is the exception. Let it be assumed that the upper limit of normal heart weight is 399 grams, a very generous allowance, and that the 25 per cent of cases in which the heart was not weighed

at necropsy also had hearts of normal size; yet 56 per cent of the series in the two years in question had hearts weighing 400 grams or more (Table I). This state was more striking in fibrotic hearts (82 per cent in nonthrombotic and 63 per cent in thrombotic disease). More than one-half of the enlarged hearts were heavier than 500 grams. It cannot be gainsaid that hypertension, which could not be assayed at necropsy, may have caused hypertrophy.

TABLE I. ANALYSIS OF 163 CASES OF CORONARY ARTERY SCLEROSIS (1938-1939) IN WHICH NATURAL DEATH WAS SUDDEN AND UNEXPECTED

EXTENT OF DISEASE					HEART WEIGHT IN GRAMS					
C	T	F	I	R	?	350	350-399	400-449	450-499	500
+					6	6	6	2	7	4
+		+			6	0	2	13	5	15
+			+		1	3	0	1	1	3
+				+	8	0	1	1	2	1
+	+				4	0	1	3	1	1
+	+		+		7	0	2	0	1	3
+	+	+			5	2	1	3	2	10
+	+	+	+		3	1	1	0	1	6
+	+			+	1	1	4	0	0	0
+	+	+		+	1	1	0	0	1	2
Total					42	14	18	23	21	45

C, coronary artery sclerosis; T, coronary artery thrombosis; F, fibrosis of myocardium; I, infarction of myocardium; and R, rupture of heart.

A brief description of the women with coronary artery disease may be in order. In our series, there was not a single case encountered until the age range, 40 to 44 years, was reached, when one subject was noted; none was found in cases between the ages of 45 and 49 years. In the ensuing half decades, the numbers were eight, eight, eleven, four, and four; there was only one case in subjects over 75 years of age. Although fatal coronary disease appears to manifest itself later in women than in men, as also found by Hallermann, the age range after fifty years furnishes more coronary artery disease in women than their proportion of the population.

SUMMARY

Among 2,030 cases of sudden and unexpected natural death autopsied over a six and one-half-year period in the Borough of Manhattan, New York City, in 45 per cent, death was attributed to diseases of the heart and aorta. Of these,

two-thirds (30.4 per cent of the 2,030 cases) were caused by coronary arteriosclerosis. This percentage of coronary artery disease in the cardiac and aortic group corresponds almost exactly with that reported from Berlin, Germany, over an eight-year period.

Sudden death from coronary artery sclerosis occurred most frequently in white men (90 per cent). The three decades between 44 and 74 years contributed one and one-half times their percentage share of the population, but sudden death from this disease began to appear in the third decade. Death took place under no specific circumstances.

In almost three-fourths (75.5 per cent) of the hearts, coronary artery sclerosis, and not fresh thrombosis, was responsible for vascular occlusion. In the remaining cases, a not always fresh thrombosis was encountered and an underlying sclerosis, usually of severe grade, was always present. It is incorrect to attribute death to coronary thrombosis without indicating the underlying primary sclerotic disease of the arteries.

Cardiac hypertrophy was found in 117 (66 per cent) of the 163 subjects whose deaths were analyzed during a two-year period. It was more prominent in the presence of myocardial fibrosis.

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AN AID FOR TAKING PRECORDIAL ELECTROCARDIOGRAMS

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THE long rubber belt usually supplied with electrocardiographs for taking precordial leads gives satisfactory results but is somewhat awkward to use. It is common practice, therefore, to dispense with this belt and have either the patient or the operator hold the exploring electrode in place. Because of unavoidable motion, however, this frequently results in some wandering of the baseline or other artifacts. The chest strap described in this communication combines simplicity and accuracy for taking precordial leads with the patient in the recumbent position.

The apparatus consists of two parts: (1) a transparent plastic strap weighted at both ends, which rests on the patient's chest and serves to hold the electrode in place; and (2) a transparent plastic block which replaces the usual electrode handle.

The chest strap is made of vinylite or similar flexible transparent plastic about 0.04 inch thick, 20 to 21 inches long, and 3 inches wide (Fig. 1). The vinylite used* was supplied in sheets roughly 18 by 48 inches in size, so that twelve strips 3 by 24 to 25 inches were obtained from each sheet.

Two weights, each between 2 and 3 ounces, are prepared. Brass plate about 2 1/2 inches x 1 1/2 inches x 1/8 inch is satisfactory. One is placed about 2 inches from each end of the plastic strap, the free ends are folded over and sealed so as to enclose these weights. Sealing can be done best by "electronic welding,"† but hand or machine stitching is satisfactory. No serviceable adhesive was found.

The plastic block can be made from Lucite or Plexiglass rod 1 inch to 1¼ inches in diameter, cut about ¾ inch thick and polished for transparency. A hole is drilled in one of the flat surfaces to receive the central pin of the exploring electrode.

Method of Use.—The chest is marked and prepared with electrode jelly in, the usual fashion. With the patient in the recumbent or semirecumbent position one of the weighted ends of the chest strap is tucked under the left back and the strap draped across the thorax so that the width of the strap covers all of the

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*This is the type of vinylite which was used by the shoe industry during the war. The material was supplied for this study by the Phillips-Premier Corp., Boston, Mass.

†The "electronic welding" was done by the Victory Plastics Co., Hudson, Mass.

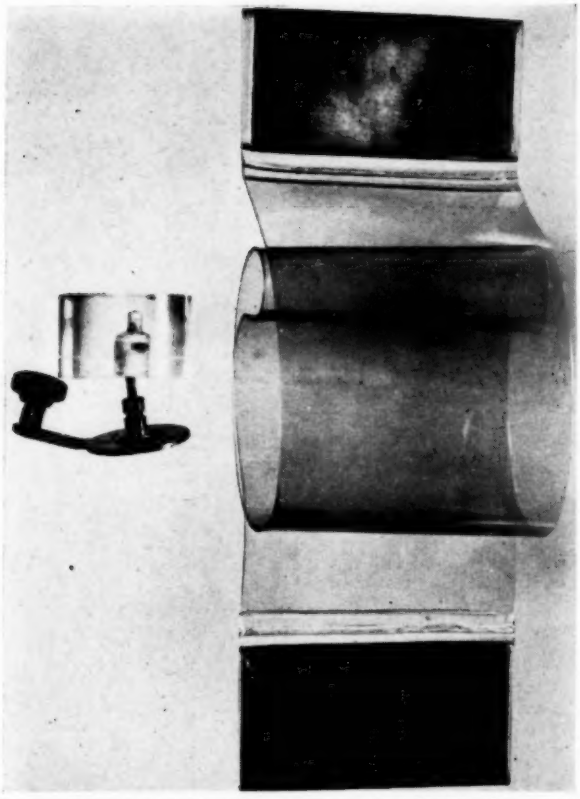

Fig. 1.—The two essential parts of the apparatus. On the right is shown the transparent plastic chest strap weighted at each end, and on the left, the plastic block fitted over the central pin of the chest electrode.

Fig. 2.—The chest strap and plastic block holding the electrode are shown applied to the chest.

marked positions and the free end lies on the right chest or in the right axilla. The block is fixed to the exploring electrode which is connected to the appropriate wire.

The free end of the strap is lifted momentarily, the electrode is placed in position, the strap is replaced, and the tracing is recorded (Fig. 2). This procedure is repeated for each precordial position desired.

The transparency of the strap and block makes it possible to see the location of the electrode at all times. When the electrode is in position, the strap rests snugly on the top of the block so as to clear the binding post and at the same time it hugs the chest and keeps the electrode in place. When taking electrocardiograms in Positions 5 and 6, especially if the breasts are pendulous, it may be advisable to place the left arm close to the side of the body. In Position 5 the electrode and block will rest just anterior to the left arm, while in Position 6 the arm will rest directly on the block.

A COMPARISON OF THE BLOOD PRESSURE IN THE LYING AND STANDING POSITIONS: A STUDY OF FIVE HUNDRED MEN AND FIVE HUNDRED WOMEN

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THE range of the normal blood pressure has been studied by several observers in the past so that the average blood pressure readings, at least for the sitting position, can be given with a high degree of accuracy.[1-3] The blood pressure has also been studied with the body in different positions.

The majority of these studies have been concerned with noting changes in the systolic blood pressure and heart rate as a means of determining physical fitness.[4-7] The response of the heart rate to exercise and the time required for the heart rate to return to its previous level has been found to be the best index of physical fitness.[8] The correlation of the change of blood pressure in different positions with physical fitness has been disappointing. Essential orthostatic hypotension has been well studied and is now considered a specific clinical entity which, at least in the minds of some investigators, is a lack of proper function of the sympathetic nervous system.[9-11] Postural hypertension has likewise been reported which might easily be the antithesis of postural hypotension, in which case overactivity of the sympathetic nervous system might well be the cause for such a reaction.[12] Renal blood flow has been found to be diminished in normal patients as well as in patients in whom a rise in blood pressure is associated with the erect posture.[13-14]

It seemed plausible, therefore, to study a large group of normal subjects to determine what happens to the blood pressure when one changes from a lying to a standing position. Such a study would tend to give clues as to the effect of the erect posture upon man; likewise, the effect of posture could be appraised as one of the factors in the etiology of early essential hypertension.

Man is one of the few animals who, undoubtedly, originally adapted to a four-legged position, has in the course of time changed his posture to that of the erect position and become the only biped of the primates.[15] This, of course, has necessitated the development of certain compensatory mechanisms; this is particularly true in the cardiovascular system. The simple act of arising from a lying position and the ability to remain in the upright position calls upon the body to perform an unusual task to overcome the force of gravity. As Hill[16] demonstrated in 1895, it is impossible to maintain most of the four-legged mammals in an upright position for any length of time without the animal dying as a

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result, primarily, of circulatory insufficiency to the brain. This is due to the fact that the cardiovascular system is unable to compensate for the effect of gravity.

In man, evolution no doubt has presented us with certain constrictor mechanisms of the blood vessels of the legs and splanchnic area to prevent a fall of blood pressure when man assumes the upright position. This, of course, enables blood to reach the brain. Man is also, I believe, the only animal who in the absence of renal disease develops hypertension spontaneously.

METHOD OF STUDY

Five hundred men and five hundred women between the ages of 18 and 55 years were examined during a routine examination. All patients were white, and all European stocks were included in the study. The group included many young men who were considered essential for their work in the war effort. The examination was done at the time of a pre-employment or periodic physical examination and was carried out in an air-conditioned room at about 72°F., usually in the late morning or early afternoon. The blood pressure was first taken in the lying position after the patient had been supine for three to five minutes, or possibly longer. At least three readings were made by rapidly inflating the cuff above the systolic pressure and listening for the first and third auscultatory sounds as described by Korotkow, or until two consecutive readings were found to be the same. The patient was then asked to sit on the examining table and the remainder of the physical examination was completed. The patient then was asked to stand at ease upon the floor. The blood pressure and pulse were measured after the patient had been standing for at least three minutes. Three consecutive blood pressure readings were made in the same manner, or until two consecutive readings were found to be similar. The last reading was then taken.

There was encountered the usual number of patients who seemed slightly agitated for no other reason than that they were being examined by a physician. A few, of course, may have been slightly apprehensive as to whether they might pass the examination for employment or for flight duty. Every effort was made, however, to put the subject at ease.

The upper limits of normal for the blood pressure readings of this study were chosen as a systolic reading of 150 mm. Hg and a diastolic reading of 90 mm. of mercury.

The cuff was inflated as rapidly as possible to avoid undue congestion of the veins in the arm, which may have a tendency to raise the diastolic blood pressure. The arm was also held so that the brachial artery was at the level of the heart, since variation of the position of the arm, especially upon standing, makes a striking change at times in the diastolic reading. Differences of 10 mm. Hg in the diastolic reading were observed merely by letting the arm drop to the side and then determining the blood pressure; with the arm at the side, the brachial artery is dependent to the heart by 10 to 15 centimeters.

Some readings were made by taking the diastolic reading first. The cuff was inflated rapidly to about 10 mm. Hg above the estimated diastolic pressure. The cuff was deflated and the diastolic reading was made. The blood pressure was then determined in the more conventional style of taking the systolic reading first and then the diastolic reading. No appreciable difference in the diastolic reading was noted, although at times the diastolic reading seemed more distinct when the diastolic reading was made first.

RESULTS AND DISCUSSION

The pertinent data from this study are presented in Tables I, II, and III. The abnormally elevated blood pressure readings were divided into seven groups, distinction being made between systolic and diastolic hypertension and as to whether the abnormality occurred in the lying or standing position, or both. The composition of the seven groups is shown in Table I.

The incidence of hypertension, diastolic and systolic, in the lying and standing positions was about equal for the groups of men and women and averaged 3.4 per cent. The incidence of diastolic hypertension alone in the lying and standing positions was even higher, and the average for the two groups was 3.9 per cent. It is interesting that nearly twice as many men demonstrated a diastolic hypertension as compared with women. It is appreciated, of course, that the

TABLE I. THE INCIDENCE OF VARIOUS TYPES OF HYPERTENSION IN THIS STUDY WITH A COMPARISON OF THE MEN WITH THE WOMEN

GROUP		MEN (PER CENT)	WOMEN (PER CENT)	AVERAGE (PER CENT)
1	Diastolic and systolic hypertension, lying and standing	3.0	3.6	3.4
2	Diastolic hypertension, lying and standing	5.0	2.8	3.9
3	Diastolic hypertension, lying only	0.8	0.2	.5
4	Diastolic hypertension, standing only	6.4	1.8	4.1
5	Systolic hypertension, lying and standing	0.4	0.4	0.4
6	Systolic hypertension, lying only	0.2	0.6	0.4
7	Systolic hypertension, standing only	.00	0.2	0.1

TABLE II. THE BEHAVIOR OF BOTH DIASTOLIC AND SYSTOLIC BLOOD PRESSURE READINGS UPON CHANGE IN POSTURE

	MEN	WOMEN	AVERAGE
Diastolic pressure increased 4 mm. or more	53%	44%	48.3%
Diastolic pressure decreased 4 mm. or more	14%	9.8%	12.0%
No appreciable change (less than 4 mm.)	33%	46.2%	39.7%
Systolic pressure increased 10 mm. or more	4.2%	3.2%	3.7%
Systolic pressure decreased 10 mm. or more	36.8%	28.8%	32.8%
No appreciable change (less than 10 mm.)	59%	68%	63.5%
Average age (years)	33.9	32.5	33.2

TABLE III. CHANGES IN THE PULSE RATE UPON CHANGE IN POSITION IN THIS STUDY. CHANGES OF AT LEAST TWO BEATS PER MINUTE OR MORE WERE CONSIDERED SIGNIFICANT

	MEN	WOMEN	AVERAGE
Average pulse rate, lying	77.3	79.3	78.3
Average pulse rate, standing	89.6	91.0	90.3
Range of pulse rate, lying	52 to 125	54 to 118	
Range of pulse rate, standing	54 to 140	60 to 148	
Average increase in pulse rate per minute on standing	13.3	13.0	13.2
Range of increase in pulse rate on standing	2 to 44	2 to 42	
Increase in pulse rate on standing	96%	94.6%	95.3%
No change in pulse rate on standing	2.4%	3.2%	2.8%
Decrease in pulse rate on standing	1.6	1.8	1.7

incidence of diastolic hypertension alone would not have been as great had the upper limit of normal for systolic blood pressure been reduced from 150 to 140 mm. of mercury. However, it should be emphasized that the diastolic reading is of much more importance than the systolic reading from the standpoint of estimating peripheral resistance, which, of course, is the important determination in hypertension. As a matter of fact, the systolic blood pressure can be disregarded to advantage in clinical medicine, at least in the study of hypertension. The practice of reporting the diastolic blood pressure and the pulse pressure would give the same information and would tend to encourage thought along more physiologic lines.

Comparison of Groups 3 and 4 of this study amply demonstrates the effect of posture upon the diastolic blood pressure, at least in those persons whose diastolic pressure hovered around 90. The occurrence of an abnormal diastolic blood pressure reading only in the standing position, as compared with the lying position, was found eight times more frequently in men and nine times more frequently in women. Comparison of the men and women in Group 4 is also of interest, as it demonstrates that diastolic hypertension, only in the standing position, was almost four times as common in the men as in the women in this group. The average of the two groups, men and women, is 4.1 per cent and even exceeds the figure for Group 2 in this study.

The incidence of what is commonly called essential hypertension (Group 1 in this study) is a rather low figure of 3.4 per cent. However, if one combines Groups 1, 2, and 4, which gives the percentage of elevated diastolic blood pressures in the standing position, the incidence is remarkably increased to 11.4 per cent. It is appreciated that certainly not all the patients in Groups 2 and 4 will eventually develop essential hypertension. Certainly the initial blood pressure reading on a patient is frequently higher than most subsequent readings, and not infrequently even exceeds the highest blood pressure reading which can be obtained with such a test as the cold pressure test. This, of course, is a nervous phenomenon resulting from the patient's nervous tension at the time of the physical examination, but it is fitting to use this bit of information in recognizing this

group of cases as patients with transient hypertension. If this is true, there seems good evidence to indicate that a higher percentage of these subjects will later develop hypertension as compared with the patients whose blood pressure remains the same or falls during such an observation.

It is of considerable importance, therefore, to observe patients with borderline blood pressure readings, particularly diastolic readings which hover about 90 mm. Hg in both the lying and standing positions, to determine the response of the diastolic pressure to the change in position. In fact, standing, alone, may be one pressor test, particularly at the time of the initial examination of the patient where both the standing position and the nervous tension of the examination will very likely produce a maximum response of the diastolic reading.

Groups 5, 6, and 7 of this study indicate the relative infrequency of systolic hypertension alone in the absence of some elevation of the diastolic pressure. The fact that the average age of the whole group was 33.2 years and that none of the patients was over 55 years of age excludes those elderly patients who have systolic hypertension as a result of an inelastic, sclerotic aorta.

From Table II one can obtain some idea as to the change in the systolic and diastolic blood pressure readings upon change of posture. A change of 4.0 mm. Hg or more in the diastolic blood pressure readings or a change of 10 mm. Hg or more in the systolic reading were arbitrarily taken as being of some significance. It is quite apparent that the diastolic reading increased approximately four times as frequently as it decreased. In approximately 40 per cent there was no change; the reverse was true of the systolic blood pressure reading. In over 60 per cent of the cases there was no appreciable change. In the majority of the remaining cases (33 per cent), however, there was a fall of the systolic pressure of 10 mm. or more. The tendency, therefore, was for the pulse pressure to decrease at the expense of a decrease in the systolic pressure, as well as of a rise in the diastolic pressure. It should be emphasized that there were cases in which there was no appreciable change of either systolic or diastolic blood pressure and a few cases in which both pressures decreased. The degree of change together with the frequency is illustrated in Fig. 1.

Table III gives the results of the observations of the pulse rate during this study. The average pulse rate for the whole group while lying was 78.3 per minute. Upon standing the average pulse rate rose to 90, and in each position the difference between the groups of men and women was probably not significant. The resting pulse rate, lying, of 78 is higher than the average basal resting pulse rate, which indicates that a certain amount of nervous tension was associated with undergoing a physical examination. It is also apparent that under the conditions of this study practically all of the pulse rates increased upon standing, since 95 per cent of the group showed this increase. The average increase was essentially the same in both the groups of men and women and amounted to 13.2 beats per minute.

Some of the patients who had either diastolic hypertension lying and standing or diastolic hypertension only while standing (Groups 2 and 4 of this study)

did show a considerably faster pulse rate than normal, but others demonstrated a perfectly normal pulse rate. However, the average for the pulse rate of Groups 2 and 4 of this study was about 96 beats per minute as contrasted with the overall average of 90 beats per minute. Although this difference is slight, it is probably significant.

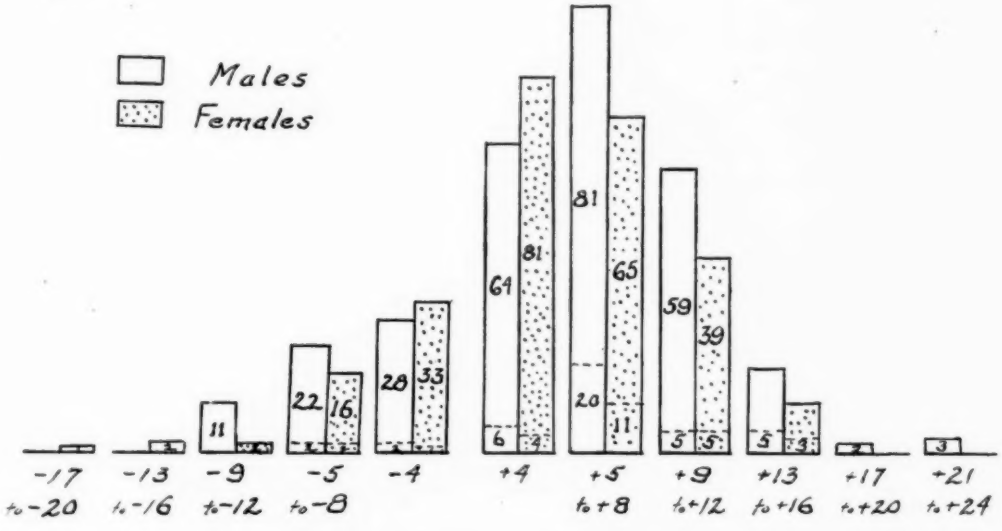

Fig. 1.—The degree and range of change in the diastolic blood pressure readings with change in posture is presented. The cases with a less than 4 mm. change are not represented. The areas below the dotted lines indicate those patients with hypertension in one or both positions. The relative shift to the right in the figure is apparent. The figures represent the number of cases.

The position of the arm is of considerable importance when taking the blood pressure, especially in the standing position.[19-21] The blood pressure, particularly the diastolic reading, has a tendency to increase with dependency and to decrease as the arm is raised above the heart. In the horizontal plane, the position of the arm does not seem to have an appreciable effect upon the diastolic blood pressure.[22] One might expect that dropping the brachial artery about 10 cm. below the heart would increase the pressure in the artery approximately 10 mm. Hg since the weight of a 10 cm. column of blood is approximately equal to the weight of a 10 mm. column of mercury, the specific gravity of blood being 1.06 and that of mercury 13.6.

In 1904 Erlanger and Hooker[23] published a rather comprehensive study of the effect of change of posture upon one normal individual and demonstrated that the vasoconstrictor element on standing could be eliminated by immersing the body when erect in water. They also demonstrated that immersion of the body in cold water had a pressor effect upon the blood pressure and that the diastolic blood pressure is nearer the mean blood pressure than is the systolic blood pressure. Wald and associates,[24] have called attention to the changes in blood pressure during the first minute of standing. After the first minute, they

found no appreciable change, indicating that the adjustment to standing is quite rapid.

During the course of this study a moderate number of Negroes were examined and the blood pressures in the lying and standing positions were compared. The number, however, proved too small to be of any significance. The comparison between white people and Negroes would be of interest because of the observation that hypertension seems to be more frequent in Negroes. Then, too, a follow-up study in ten or twenty years of the patients in this report with borderline blood pressure readings, particularly in the standing position, would be of the utmost importance in evaluating the role of posture as a factor in the etiology of essential hypertension.

The possible relationship between the vertical stance of man and essential hypertension is an interesting one. Since the diastolic blood pressure reading gives the best index we have of peripheral resistance, it is pertinent to know under what conditions in man the diastolic blood pressure is enhanced. It is true that many human beings are able to make the compensatory adjustment to the erect posture without appreciable change in the diastolic blood pressure; in fact, there are some subjects in whom the diastolic pressure falls somewhat upon standing. In about one-half of the individuals in this study the diastolic pressure increased upon standing. Since man spends about one-half to two-thirds of his time in the erect or semierect position each day, it is conceivable that over a period of years the increment in the diastolic blood pressure in the vertical stance is an important factor in the gradual increase in peripheral resistance. Nervous stimuli, pain, and cold are also important factors which will raise the diastolic blood pressure of man. It may be that a combination of several factors results in gradually raising the peripheral resistance to the blood flow in man and it seems logical to assume that the vertical stance is one of these factors. Perhaps this is the price that a certain percentage of human subjects have to pay for being bipeds.

If lumbodorsal sympathectomy produces essentially a postural hypotension, one might expect men to have a greater chance of benefit than women, since from this study it would seem that the diastolic blood pressure is more frequently raised in men than in women upon standing. This has not, however, been the experience with sympathectomy for hypertension, in which case women seem to have better results than men.

SUMMARY

1. Observations were made on 1,000 healthy individuals (500 men and 500 women) between the ages of 21 and 55 years with respect to the change in blood pressure in the lying and standing positions. The incidence of both diastolic and systolic hypertension, lying and standing, was found to be 3.4 per cent.

2. The presence of diastolic hypertension (lying and standing) was found, however, to be more common than essential hypertension, the incidence being

3.9 per cent in this study. Nearly twice as many men as women were found to demonstrate diastolic hypertension.

3. The presence of diastolic hypertension in the standing position alone was found to be even more frequent, averaging 4.1 per cent with a sex ratio of about 3.5 men to one woman.

4. The possible role of the erect posture as one of the factors in essential hypertension is considered.

Acknowledgment is made to Dr. Paul D. White for helpful criticisms and suggestions.

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Clinical Reports

MYOCARDIAL INFARCTION IN A TWELVE-YEAR-OLD BOY WITH DIABETES

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A REVIEW of recent literature emphasizes that more and more frequently coronary disease is being recognized and diagnosed in young adults.[1-8] However, coronary occlusive disease can also occur in infants and children, as Stryker points out in a review of the subject.[9] Because of the relative rarity of such lesions, the clinical history of myocardial infarction in a 12-year-old boy with diabetes mellitus is reported.

CASE REPORT

H. R., a white boy 12 years of age, was admitted to the Wayne County General Hospital and Infirmary on Sept. 17, 1945, in a semicomatose state. The only history available was that he had been a known diabetic since the age of 2 years. His diet was uncontrolled, except for the restriction of sweets, and he took 15 units of protamine zinc insulin before breakfast. For a few days prior to admission he had been sneezing and coughing, and on the day of admission he complained of a pressure sensation across the chest.

A more detailed history was obtained later which revealed that throughout childhood he had had frequent head colds, tonsillitis, and pharyngitis. Every since the discovery of the diabetes, he had migratory joint pains and frequent epistaxes. From 1940 to 1943, he had repeated hospitalizations for the regulation of his diabetes. In 1943, he had a mild attack of scarlet fever but recovered without complications. For the past one to two years, the parents had noted dyspnea on mild exertion and slight ankle edema. On Sept. 1, 1945, after eating a good meal, the child suddenly experienced severe, constricting pain under the middle of the sternum and had severe dyspnea and orthopnea.

The family history was unremarkable except for the death of two siblings, one being stillborn and the other dying on the first day of life. Three other siblings were living and well. A paternal cousin had diabetes mellitus.

At the time of admission, the temperature was 97.6° F., the respirations were 30 per minute, and the pulse rate was 130 per minute. The systolic blood pressure was 135 mm. Hg; the diastolic pressure was unobtainable. The patient was a pale, very small but fairly well-proportioned boy of 12 years, conscious but lethargic. His breathing was Kussmaul in type. The pupils were irregular, round, and equal. Funduscopy was negative. The pharynx was injected and the tonsils were large and slightly reddened. The chest was clear to percussion and auscultation. The heart was enlarged to the left and the left border of cardiac dullness was 2.5 cm. beyond the midclavicular

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line in the fifth intercostal space. The aortic second sound was louder than the pulmonic second sound. No cardiac murmurs were heard and normal sinus rhythm was present. There was an increased area of gastric tympany.

On admission, the blood sugar was 600 mg. per cent and the nonprotein nitrogen was 60 mg. per cent. The carbon dixoide combining power was 7 volumes per cent. The urine showed 4 plus sugar and the presence of acetone. The differential blood count showed 58 polymorphonuclear leucocytes, of which 31 were filamented and 27 nonfilamented, 29 lymphocytes, 9 monocytes, 1 basophil, 2 metamyelocytes, and 1 myelocyte. There was toxic graulation of the polymorphonuclear leucocytes.

Gastric aspiration done on admission recovered 1,500 c.c. of fluid. In the first six hours of treatment the child received 3,000 c.c. of intravenous fluid containing 250 grams of glucose and 135 units of crystalline zinc insulin. During this period, the carbon dioxide combining power rose from 7 volumes per cent to 46 volumes per cent and at the end of eighteen hours, only a trace of acetone remained in the urine (Table I).

TABLE I. LABORATORY FINDINGS

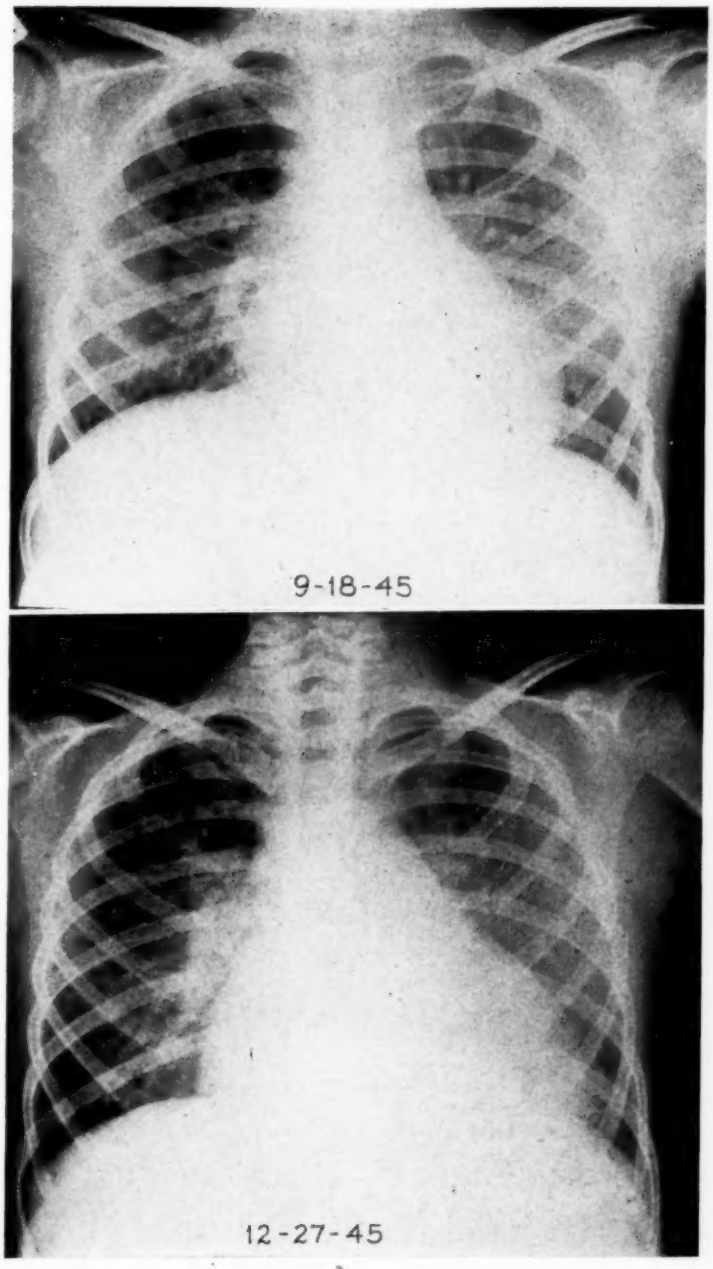
Urinalyses

DATE	SP. GR.	ALB.	SUGAR	ACETONE	MICROSCOPIC
9/17/45	——	++++	Tr.	+	Occ. WBC. No organisms in stained sediment
9/27/45	1034	+	++++	0	Many gram-neg. bacilli, few micrococci and gram-pos. diplococci
10/ 6/45	1030	+++	0	0	2-3 hyaline casts; 4-6 WBC.
10/ 8/45	1019	0	0	0	Neg. except for few gram-pos. cocci
12/11/45	1022	++	0	0	4-6 hyaline casts, 3-4 WBC, 1-2 RBC
12/15/45	1011	+	0	0	3-4 WBC, 1-2 RBC
12/19/45	1028	++	++++	0	3-4 hyaline casts, 4-8 WBC, 1-2 RBC.
2/ 6/46*	1013	+++			Occ. WBC and RBC. Numerous granular and occ. hyaline casts

During this same period, the temperature rose from 97.6° F. rectally to 102.4° F., and the pharynx became red and edematous. The chest was clear to percussion and auscultation and there was no edema peripherally. The blood pressure fell to 90/55. A transfusion of 200 c.c. of whole blood was given and intramuscular penicillin in doses of 20,000 units every three hours was started. The following day, a roentgenogram of the chest showed early bronchopneumonia, pleurisy on the right, and an enlarged heart (Fig. 1). At this time, the patient complained of substernal pain on deep inspiration.

During the next week, the temperature continued elevated. Râles and dullness at the bases of both lungs persisted. There was occasional acetonuria and persistent glycosuria. Therefore, efforts were made to regulate the diabetes by small daily doses of protamine zinc insulin and crystalline insulin administered before meals according to the reaction of the urine.

A.



B.

Fig. 1.—*A*, Roentgenogram of chest showing pleurisy on right, early bronchopneumonia and enlarged heart. *B*, Roentgenogram of chest suggestive of passive congestion of both lung fields. Pleura thickened at both margins.

Blood Counts

DATE	HB. GMS.	WBC	DIFFERENTIAL							
			PMN	F	NF	L	M	B	E	
9/17/45	15	49,100	58	31	27	29	9	1		1 myelocyte 2 metamyelocytes
9/27/45	12.7	11,550	72	65	7	19	8			
10/10/45	13.5	9,200								
10/29/45	13	5,200	51	51	0	29	15		5	
12/ 7/45	13	9,150	65	63	2	32	3			
2/ 6/46*	11	15,150	69	61	8	27	2	2		

Blood Chemistry

DATE	GLUCOSE	NPN	CHOLESTEROL	CO_2	SERUM PROTEIN
9/17/45 11:00 A.M.	600	60		7	
1:30 P.M.	695			21	
8:30 P.M.	62			77	
9/29/45		32	190		
10/ 2/45					5.3
10/ 8/45	170	69			
10/11/45	56	41			
11/ 2/45	323				
12/ 7/45	120	50			
12/ 8/45	37	34		60	Albumin 2.5, globulin 2.9
12/15/45	250				
12/21/45	135				

*Information from records at Detroit Receiving Hospital.

On Sept. 15, 1945, the râles had disappeared from both lungs, but a pericardial friction rub developed at the cardiac apex and a reduplicated second sound was noted at the base of the heart. The legs were markedly edematous. An electrocardiogram taken the following day showed tachycardia and evidence of an extensive anterior myocardial infarct. See Fig. 2 for serial changes.

On Sept. 26, 1945, a roentgenogram of the chest was interpreted as showing congestion of the lung fields with a slight effusion present on the right side. The cardiac configuration was suggestive of mitral disease. The friction rub had disappeared. The patient was digitalized. Two days later, the right chest showed definite physical signs of pleural fluid and the liver was felt three fingerbreadths below the right costal margin.

Because signs of pleural fluid persisted, a thoracentesis was performed on Oct. 2, 1945, and 150 c.c. of serous fluid was removed from the right pleural cavity. Its specific gravity was 1.010 and culture and smear were negative for any organisms. At that time, a roentgenogram was taken which indicated that the greatest transverse diameter of the heart had increased 1.5 centimeters. The possibility of a pericardial effusion was considered. Because of persisting gener-

alized edema, 0.5 c.c. of Mercuhydrin was given intramuscularly on Oct. 6, 1945, which caused a satisfactory diuresis with a diminution of the ascites and the pleural effusion. The ankle edema disappeared and for the first time the child was afebrile.

Although the urine was kept acetone-free, the diabetes was poorly stabilized; the fasting blood sugars varied from 56 mg. per cent to 323 mg. per cent. On Nov. 17, 1945, the patient was discharged with instructions to eat a salt-free weighed diet and to take 20 units of protamine zinc insulin and 20 units of crystalline zinc insulin before breakfast, 5 units of crystalline zinc insulin before lunch, and 15 units of crystalline zinc insulin before supper.

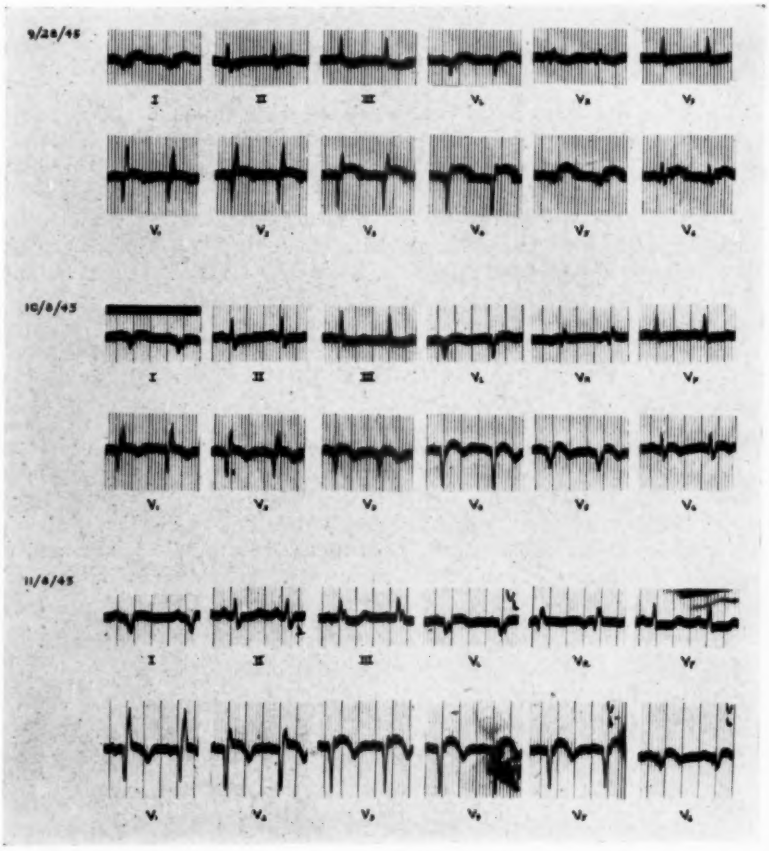


Fig. 2.—Electrocardiograms showing the standard, precordial, and extremity leads. The QRS and T-wave changes suggesting infarction are most prominent in the chest leads.

On Nov. 29, 1945, the patient was seen in the outpatient clinic of this hospital where it was learned that because his appetite had failed immediately upon going home, the parents had attempted the regulation of the insulin dosage. His fasting blood sugar on that day was 133 mg. per cent. On examination, the left heart border was at the anterior axillary line and a systolic murmur and a split second sound were heard over the entire precordium, but best heard at the apex. The chest was free of râles; the liver was slightly enlarged, but no edema was noted.

On Dec. 6, 1945, the patient was readmitted to this hospital with edema of the entire body and ascites which first became evident on Dec. 1, 1945, following a severe insulin reaction. The essential physical findings at that time were: retinal edema, crystalline retinal exudates, and an

increased arteriovenous ratio. There was decreased resonance at both lung bases, with no change in the breath sounds. There was marked ascites and a 4 cm. enlargement of the liver by ballottement. The patient had bilateral costovertebral angle tenderness with marked edema of the penis, scrotum, and lower extremities. The fasting blood sugar was 180 mg. per cent and the nonprotein nitrogen was 50 mg. per cent.

During the next week, the diabetes was well controlled on a salt-free diet plus crystalline zinc insulin before meals. Because of marked respiratory distress and a rapid heart rate, on Dec. 11, 1945, the patient was redigitalized, given 0.5 c.c. of Mercuhydrin intramuscularly, and oxygen. From Dec. 12, 1945, on, the patient had periods of delirium which came on at about 6:30 P. M. each day. The insulin dosage was reduced with some improvement in the symptoms but the patient continued to complain nightly of substernal and left shoulder pain. On Dec. 29, 1945, the parents removed the child from the hospital against medical advice.

On Feb. 2, 1946, the patient entered The Detroit Receiving Hospital.* Since leaving Wayne County General Hospital and Infirmary, there had been a gradual increase in anasarca until one week before admission, when it had increased rapidly. This was somewhat relieved by an injection given by a local physician which caused marked diuresis. During the week preceding his final hospital admission, he also had an upper respiratory infection. On Feb. 1, 1946, he had constant sharp precordial pain which radiated down the left arm. On admission to The Detroit Receiving Hospital, the physical examination was essentially the same as previously described, except for the following: the fundal vessels showed an arteriovenous ratio of 1:2; there was arteriolar spasm but no sclerotic changes. There were small linear and round hemorrhages, and retinal edema was marked. The chest showed decreased tactile fremitus in the right axilla and deceased resonance to percussion throughout. The cardiac findings were as previously described. The blood pressure was 135/100.

For the next two to three days, following mercurial diuresis, he seemed to improve but on Feb. 6, 1946, he coughed up a small amount of bright red sputum. Inspiratory and expiratory râles were heard in the right midaxilla and at the right lung base. A roentgenogram showed "diffuse soft peribronchial reaction throughout lung fields with consolidation of the right upper lobe. There is minimal pleural thickening of right lateral chest wall." Intramuscular penicillin therapy was begun but the patient expired on Feb. 6, 1945. Permission for autopsy was refused.

The final diagnoses were (1) terminal bronchopneumonia, (2) cardiac decompensation, (3) old anterior myocardial infarction, (4) diabetes mellitus, and (5) chronic glomerulonephritis.

SUMMARY

A case of myocardial infarction occurring in a 12-year-old boy with diabetes mellitus is reported.

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SUCCESSFUL TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH STREPTOMYCIN

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REPORTS of the successful use of streptomycin in the treatment of subacute bacterial endocarditis have appeared in the literature, but they are rare.[1] Priest and McGee[2] were successful with the drug in eradicating the endocardial infection in two patients but failed in a third. The infecting organism in all three was a pleomorphic streptococcus, the earliest and most pleomorphic forms being gram negative and the older forms, which appeared as pairs and short chains of cocci, being gram positive. Later, however, after the culture had been frozen, the organism grew as a typical *Streptococcus viridans* (type not specified) with a green hemolytic zone. In all three cases, the organism appeared to be highly resistent to penicillin but sensitive to streptomycin. In one, the drug could not be obtained until the last five days of the patient's illness, but at autopsy no bacteria could be demonstrated on the scattered remnents of fibrin on the valves involved.

Cady and Allen,[3] and Cady and Hunter[4] reported the unsuccessful treatment of subacute bacterial endocarditis due to *Streptococcus viridans* fecalis with streptomycin. That the drug can be used effectively in this type of infection is illustrated by the following case report.

REPORT OF CASE

M. S., a 50-year-old white housewife, was admitted to the hospital Nov. 11, 1946, complaining of weakness and fever. She denied any serious illnesses in the past, except the usual childhood diseases, and there was no history suggestive of any part of the rheumatic diathesis. She felt that she had enjoyed unusually good health all her life until ten weeks prior to admission when she suddenly became ill with fever, chills, sore throat, and generalized aching. Her family physician treated her symptomatically for influenza for one week. Fever had subsided at the end of a week, but she felt unusually weak, and after several days she discovered that she was running a low-grade, daily afternoon temperature elevation. During the ensuing weeks she became progressively weaker; fever became continuous, she suffered from drenching night sweats, and lost about twenty pounds in weight. Three weeks before admission she had taken two tablets of one of the sulfonamides every four hours for four days without noticeable improvement in her fever or general condition. At this time she noticed rapidly progressive exertional dyspnea which was promptly followed by moderate orthopnea, but there had been no precordial pain, palpitation, paroxysmal dyspnea, or edema. She began to suffer from occasional bouts of moderate epistaxis, and on several occasions she noticed the appearance of subcutaneous bleeding without known trauma. The patient's vision had been blurred for several weeks, and she complained also of floating scotomata. Review of systems, past history, and family history were irrelevant.

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Physical examination revealed a thin, pale, white woman of stated age lying quietly in a semi-Fowler position and appearing chronically ill. The skin was dry and essentially clear. The tips of several of the fingers were tender, but no splinter hemorrhages were seen, although several days later they were abundant. Petechial hemorrhages were present on the soft palate and in the left conjunctival sac, but none were found on the skin. The head was essentially negative. The pupils were equal, regular, and normally reactive. The nerve heads were well outlined and the vascular pattern was essentially normal, but there were numerous old and fresh round, flame, and crescent-shaped hemorrhages in both eyes. The ears, nose, and throat were essentially normal, and the sinuses transilluminated well. A few lower remaining teeth appeared in good condition. The tongue was normal and the pharynx clean.

The peripheral nodes were not remarkable except for a few small, shotty nodes beneath the angle of the jaw bilaterally. The trachea was in the mid-line; there was no tug, and the thyroid was not palpably enlarged.

The chest expanded equally and symmetrically. The percussion note was resonant throughout and the breath sounds were soft and vesicular everywhere. No râles, rhonchi, or friction rubs were heard. The heart apparently was slightly enlarged to the left but the aorta did not seem to be uncoiled or dilated. The waistline was not obliterated to percussion. There was considerable precordial activity and a suggestion of a systolic thrill at the apex. The rate was 110 per minute and the rhythm was regular. There was a harsh, Grade 2 systolic murmur heard best at the apex but transmitted well over the entire precordium and heard easily in the axilla and at the angle of the left scapula. The first sound at the apex was not accentuated. The pulmonic and aortic second sounds were equal and neither was appreciably increased. There was no gallop or friction. Diastolic murmurs were not heard at this time in any position. The blood pressure was 140/70 in both arms. The peripheral vessels were not appreciably thickened and the venous pressure appeared normal clinically.

The abdomen was soft and scaphoid. There was no tenderness. The liver, kidneys, and masses could not be felt, and attempts to palpate the spleen were unsuccessful. There were no costovertebral angle tenderness, sacral edema, or hernias. Pelvic examination revealed a marital introitus with good support. The pelvic examination was negative.

The extremities were essentially negative except for finger tenderness as already noted. Neurological examination was essentially normal. All deep and superficial reflexes were generally hyperactive.

Repeated examinations of the urine were normal except for occasional showers of red cells. Examination of the blood showed 7 Gm. of hemoglobin (Sahli), 2,750,000 erythrocytes, 5,150 leucocytes with 7 juvenile forms, 16 band forms, 62 segmented neutrophiles, and 15 lymphocytes. There were about 30,000 platelets per cubic millimeter; the bleeding time was prolonged and the coagulation time was normal. Prothrombin time was eighteen seconds (control sixteen). Culture of the blood on five successive days consistently yielded a luxurious growth of *Streptococcus viridans*, type fecalis.

Roentgenologic examination of the heart revealed slight enlargement in the region of the left ventricle but there was no enlargement in the region of the left auricle. The lung fields were entirely clear and bright. Electrocardiographic studies were normal.

The patient was studied for five days without any specific type of treatment. During this time a short, high-pitched, early diastolic murmur became clearly audible at the apex. Several transfusions of whole blood were then administered and she was started on 50,000 units of penicillin intramuscularly every three hours. This was increased to 100,000 units after forty-eight hours and again to 250,000 units every three hours after another forty-eight hours, because the smaller doses were without effect on her temperature curve, which ranged between 100 and 103.6° Fahrenheit. This was followed by a prompt drop in the temperature to near normal levels for the following ten days. The blood became sterile, but she continued to look unwell. Tachycardia

persisted, she continued to have drenching sweats, and she appeared much weaker than on admission. At this time, it was determined that the organism was completely resistent to penicillin through 5 units per cubic centimeter, but sensitive to streptomycin at 6 units per cubic centimeter. Streptomycin was started intramuscularly in equally divided four-hour doses totalling 1.5 Gm. every twenty-four hours. The temperature rose to 102°F. the following day and the blood culture yielded a scanty growth of the same organism. The drug was then increased to 3.0 Gm. daily and was continued at that level for the following nineteen days. The temperature returned to normal within two days. The blood cultures became consistently sterile and have remained so to date, six months following discontinuance of the drug. Her general condition began to improve and she felt better in every way. On the tenth day of streptomycin therapy she began to notice vertigo on side-to-side movements of the head which gradually increased in severity until she was constantly dizzy by the nineteenth day. This complication became so marked and receded so slowly after streptomycin was discontinued that she was unable to sit in a chair until sixteen days later and even now (six months later) she is unable to walk without assistance. Because of beginning signs of left-sided heart failure, digitalization was carried out on the forty-seventh hospital day, seven days after streptomycin treatment had ceased. Convalescence since that time has been retarded only by vertigo and she is now doing part of her housework each day. Digitalis, however, remains necessary for cardiac compensation.

SUMMARY

A case of subacute bacterial endocarditis due to *Streptococcus viridans*, type fecalis, is presented.

Inasmuch as the patient did not do well clinically on penicillin and because it was impossible to obtain blood levels sufficiently high to inhibit the growth of the organism as indicated by in vitro sensitivity tests, it seems likely that streptomycin was responsible for the eradication of the infection.

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ELECTROCARDIOGRAPHIC ABNORMALITIES IN A CASE OF UREMIA MANIFESTING HYPERPOTASSEMIA

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ALTHOUGH the electrocardiographic manifestations of hyperpotassemia have been studied in detail in animals, only a few such studies have been recorded for man.[5-7,9,10,12,13] The present case is reported because it provides perhaps an unusually clear demonstration of certain electrocardiographic changes in a uremic syndrome in which hyperpotassemia supervened.

CASE REPORT

W. R. (U. H. No. 771439), a 22-year-old, unmarried, white blocklayer was admitted to the medical service of the University of Minnesota Hospitals on Sept. 20, 1946. He complained chiefly of blurred vision and severe headache.

In 1943, while the patient was a member of the Coast Guard, he experienced an episode of soreness of the throat followed by abdominal pain and red urine. After eight weeks of hospitalization, he was discharged from the Coast Guard. He was then asymptomatic until November, 1944. At that time he is said to have developed pneumonia and to have had microscopic hematuria. Recession of symptoms was again noted until three months prior to admission. At the former time, the patient noted the onset of severe, persistent, occipital headaches which radiated over the entire head. About two months prior to admission, puffiness of the face (about the eyes) and of the legs became manifest. During the three-week period prior to admission, diminishing visual acuity and ocular pain became troublesome. The headaches persisted, but the puffiness had disappeared prior to admission. There was no history of nocturia or of dysuria.

The patient was well developed and well nourished. Oral temperature was 98.2° Fahrenheit. The heart rate was 120 per minute. The respiratory rate was 22 per minute. Examination of the ocular fundi showed bilateral papilledema and numerous areas of hemorrhage and exudate. The examination of the heart showed the point of maximum impulse to be in the sixth left intercostal space at the midclavicular line. The rhythm was regular. Reduplication of the first apical sound and a soft apical systolic murmur were noted. The aortic second sound was of tambour quality. The blood pressure was 170/120. Examination of the lungs and abdomen was negative. Slight costovertebral angle tenderness, bilaterally, was noted. The knee jerks and ankle jerks were hyperactive and equal. The Babinski sign was present bilaterally.

Numerous urinalyses were done. Specific gravities, uncorrected for albumin, ranged from 1.009 to 1.020. Plus 2 albuminuria was recorded on numerous occasions. Granular casts were found on Oct. 4, 1946. Occasional leucocytes and erythrocytes were present in the urine sediments. Urine culture on Sept. 21, 1946, was reported positive for micrococci and diphtheroids. The hemoglobin concentration on Sept. 20, 1946, was 7.0 grams per 100 c.c.; erythrocyte count was 2,100,000. Leucocyte count was 8,700 with 80 per cent neutrophiles; 17 per cent lymphocytes; and 1 per cent each of monocytes, eosinophiles, and basophiles. The hemoglobin and erythrocyte

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levels remained essentially the same during the hospital stay. Leucocyte counts of 13,000 and 15,000 were recorded on Oct. 1, and on Oct. 4, 1946, respectively. High neutrophilic percentages (to 96) were present on the latter dates. Sternal marrow biopsy on Sept. 25, 1946, demonstrated "generalized marrow hyperplasia with inflammatory changes, and a relative increase in cells of the erythroid series." Venous pressure was 10 cm. H_2O on Sept. 21, 1946. Total plasma proteins were 4.9 grams per 100 c.c. on Sept. 21, 1946, and serum cholesterol was 354 mg. per 100 c.c. on Sept. 23, 1946. The blood urea nitrogen concentration varied from 86 mg. per 100 c.c. to 236 mg. per 100 c.c. (Chart I). The creatinine range was 13.0 mg. per 100 c.c. to

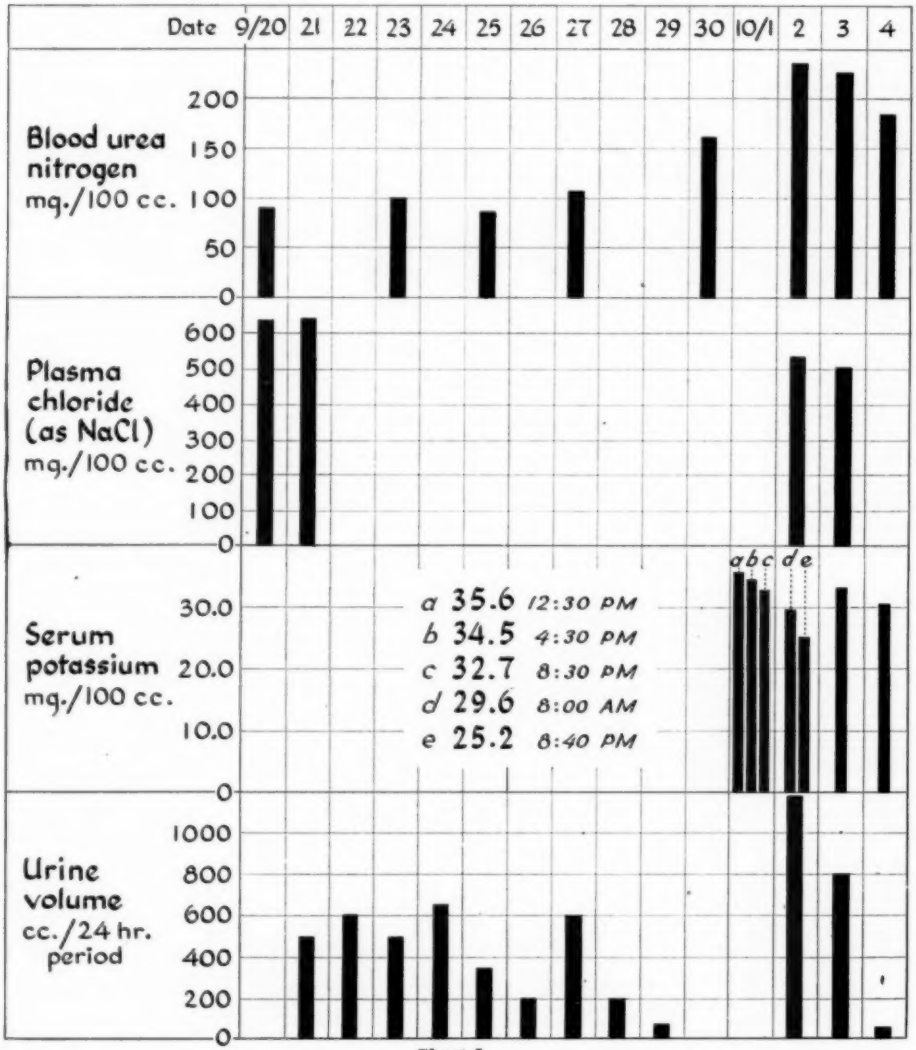

Chart I.

30.5 mg. per 100 c.c. of blood. The uric acid concentration was 5.9 mg. per 100 c.c. of blood on Sept. 23, 1946. The blood glucose concentration was 92.0 mg. per 100 c.c. on Sept. 21, 1946. The range of carbon dioxide combining power of the plasma was 32 to 44 volumes per cent. The serum chloride concentrations (as sodium chloride) were 636 mg. per 100 c.c. and 648 mg. per 100

c.c. on September 20 and 21, respectively; on October 2 and 3, they were 531 mg. per 100 c.c. and 502 mg. per 100 c.c., respectively (Chart I). The serum calcium concentration was 10.1 mg. per 100 c.c. on September 23 and 9.0 mg. per 100 c.c. on October 2. The serum phosphorous was 6.8 mg. per 100 c.c. on September 23 and 21.0 mg. per 100 c.c. on October 2. The range of serum potassium levels was 25.2 mg. per 100 c.c. (6.4 meq. per liter) on October 2 to 35.6 mg. per 100 c.c. (9.1 meq. per liter) on October 1 (Chart I).* Control serum potassium determinations ranged from 15.7 mg. per 100 c.c. to 21.6 mg. per 100 cubic centimeters.† An x-ray film made on Sept. 21, 1946, was interpreted as showing left ventricular enlargement.

Patient was afebrile aside from occasional oral temperature readings of 100° Fahrenheit. Blurring of vision and headaches continued throughout the hospital stay. Vomiting, hematemesis, hemoptysis, and epistaxis occurred intermittently. Sudden severe dyspnea and pulmonary edema supervened on Sept. 28, 1946. This episode appeared to respond to intravenous digoxin, morphine, tourniquets, and oxygen. Twenty-four-hour urine outputs are depicted in Chart I. On Oct. 1, 1946, the presence of apparent anuria for the preceding twenty-four to forty-eight hours brought to mind the possibility of hyperpotassemia.[8] Blood samples for potassium determination were drawn and electrocardiographic studies undertaken. The anuria, supposedly extant on September 30 and October 1, may have been spurious in view of the removal of 1,185 c.c. of urine by catheter on the morning of October 2.

Therapeutic measures consisted of a low protein-low salt diet, barbiturates, paraldehyde, morphine, codeine, atropine, salicylates, penicillin, digitalis, parenteral vitamin B complex, parenteral fluids, and blood transfusion. Pulmonary edema, which followed blood transfusion, prompted the use of 0.25 mg. of digoxin intravenously on September 28. Four cubic centimeters of Digalen (Lilly) were given intramuscularly on September 29 and 30. Two cubic centimeters were given on October 1 and 2. Four cubic centimeters of Digalen were again given on October 4 and 5. No potassium salts were prescribed.

For the most part, the blood pressure readings were 160/100 to 210/150. For about thirty hours prior to death, blood pressure levels within the normal range were found. Repeated examinations revealed no paresis or paralysis. Spasticity, bilateral sustained ankle clonus, markedly hyperactive and equal ankle and knee jerks, and bilateral, abnormal great toe signs were observed on October 1. The patient died at 4:40 A.M. on Oct. 6, 1946. No accurate record of the mode of death is available. Necropsy permission was not obtained. The clinical diagnosis was chronic glomerulonephritis.

Electrocardiographic Findings.—The electrocardiogram of September 21 (Fig. 1) was interpreted as possibly a rather atypical instance of left ventricular strain. The possibility of pericarditis or of recent myocardial infarction was likewise entertained. The electrocardiogram of September 26 (Fig. 1) manifested T-wave changes and slightly increased QRS duration, which together might be regarded (in retrospect) as evidence of potassium effect. The electrocardiogram of September 28 appears to present a stage intermediate between the findings of the two preceding tracings. The electrocardiogram of Oct. 1, 1946 (Fig. 1) was taken in the midst of a period of urinary suppression (Chart I). Intraventricular block, huge peaked T waves, and first degree atrioventricular block have become manifest. A serum potassium determination performed on blood taken simultaneously was 35.6 mg. per 100 cubic centimeters. The tracing made at 8:30 P.M. on October 1 (Fig. 1) demonstrates diminution in severity of intraventricular block, diminution in P-R interval, and receding T-wave changes. The next tracing (Fig. 2), taken on the afternoon of October 2, is characterized by changes of the same general quality as those noted at 12:30 P.M. on October 1 (Fig. 1). The serum potassium level on the morning of Oct. 2, 1946, had decreased considerably, as shown in Chart I. The serum potassium level thirty minutes prior to the electrocardiogram on the evening of October 2 was recorded as 25.2 mg. per 100 cubic centimeters. This tracing shows a marked recession of QRS and T-wave changes, disappearance of

*The method of potassium determination is based on a modification of the methods of Kramer and Tisdall and of Breh and Gaebler, quite similar to the method described by Wood.[19] Our range of normal is 17.7 to 22.2 mg. per 100 c.c. of serum.

†One millimole of K=1 meq. of K=39.1 mg. of K.

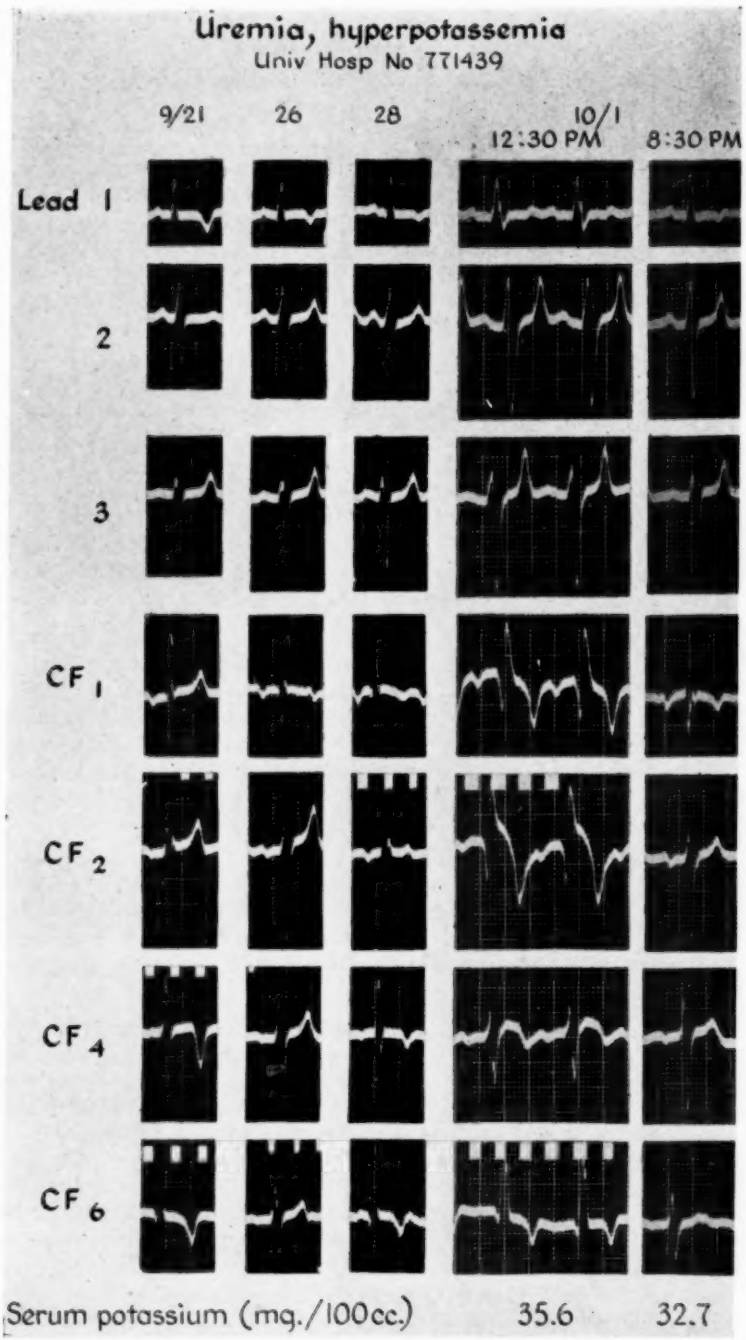

Fig. 1.—Sept. 21, 1946: P-R interval is 0.16 sec.; QRS duration (limb lead), 0.09 sec.; and Q-T interval, 0.37 second. The T waves of Lead I, CF_4, and CF_6 are inverted. The T wave of Lead CF_4 is peaked.

Sept. 26, 1946: QRS, 0.10 second; increased T-wave positivity; T_2 and T_3 peaked. The T wave of Lead CF_2 is tall and peaked. T waves of Leads CF_4 and CF_6 have become upright.

Sept. 28, 1946: Recession of T-wave contours.

Oct. 1, 1946 (12:30 P.M.): Serum K 35.6 mg. per 100 c.c.; P-R, 0.24 sec.; P_2 and P_3 abnormally wide. P_3 barely discernible. QRS_2 0.14 sec., T_1 upright; T_2 and T_3 are very tall, peaked, and have relatively narrow bases. Q-T is 0.38 second. In Lead CF_1 there is a deep Q; S-T is slightly depressed; and T is inverted and peaked. In Lead CF_2: there is a deep Q; abnormal S-T elevation which blends imperceptibly with a deeply inverted, peaked T wave. In Lead CF_4: S-T segment is + 2.5 mm.; inverted T wave. In Lead CF_6: T is inverted, peaked; slight S-T depression.

Oct. 1, 1946 (8:30 P.M.): Serum K 32.7 mg. per 100 c.c.; P waves are normal in duration. Q-T is 0.36 sec.; S-T_1 shows upward bowing. T_1 is inverted. T_2 and T_3 are less prominent. Striking chest lead abnormalities have receded considerably.

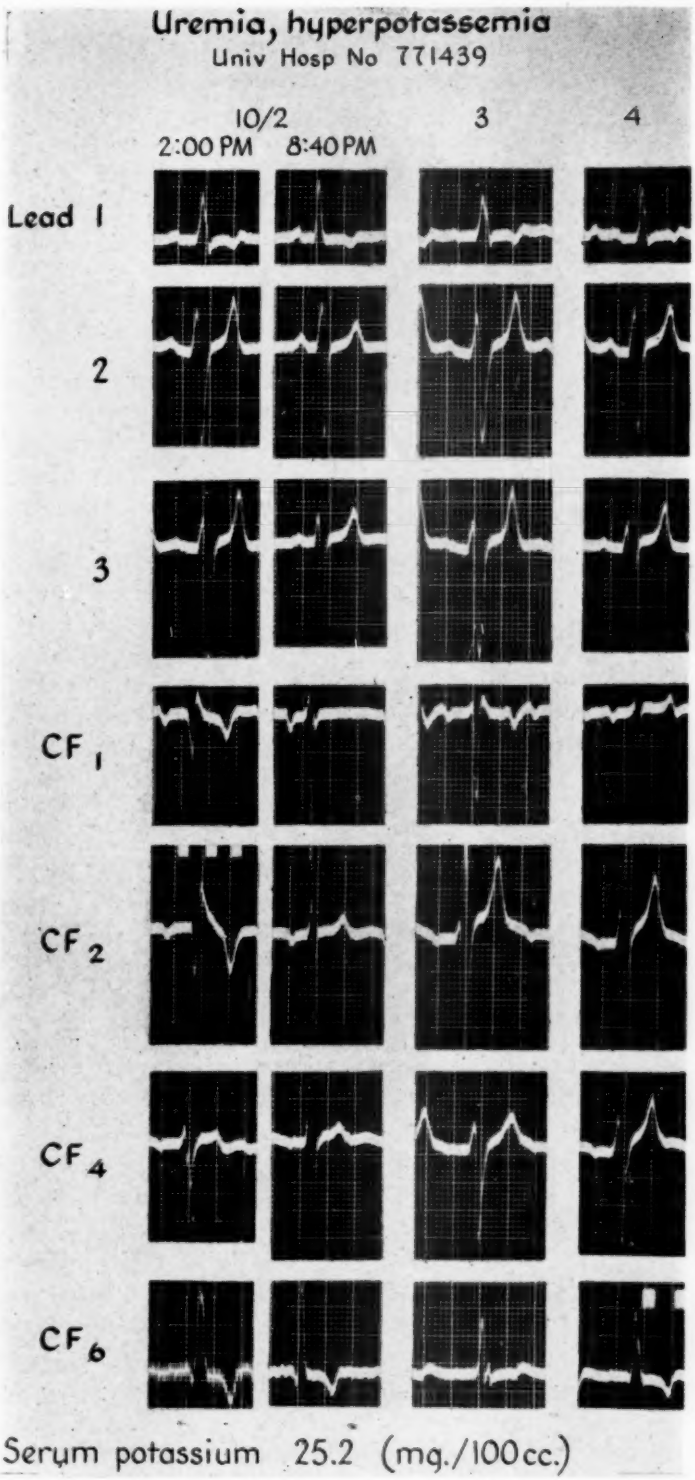

Fig. 2.—Afternoon of Oct. 2, 1946: Reversion to the relatively advanced abnormalities of October 1 (Fig. 1).

Evening of Oct. 2, 1946: Serum K 25.2 mg. per 100 cubic centimeters. Recession of changes apparent in preceding tracing associated with fall in serum K level. Oct. 3, 1946 (10:30 A.M.): Restoration of findings consistent with increasing serum potassium concentration. Oct. 4, 1946: Tracing taken about thirty-six hours before death.

prolonged P-R interval, and a general trend toward the findings of September 28 (Fig. 1). The recurrent conduction disturbances and T-wave abnormalities apparent in the tracing of October 3 (Fig. 2) are probably correlated with a rising serum potassium level (Chart I). On October 4, the serum potassium was 30.8 mg. per 100 cubic centimeters. An electrocardiogram taken on the afternoon of that day (Fig. 2) manifests changes, less pronounced on the whole, than those evident in the preceding tracing.

COMMENT

The salient electrocardiographic abnormalities presented by our patient were: (1) Peaked T waves of large amplitude and relatively brief duration in Leads II and III. These T waves were either inverted or upright in the CF leads; (2) delayed intraventricular conduction; (3) delayed intra-auricular conduction, prolonged P-R interval, and some tendency to disappearance of the P waves (especially in Lead III); (4) the development of a deep Q deflection in CF_2; (5) abnormal S-T elevation, notably in CF_2; (6) variable, changing pattern of abnormalities possibly related to corresponding fluctations in the degree of hyperpotassemia; and (7) tendency to left ventricular strain.

The first three abnormalities are similar to those ascribed to potassium intoxication in man and in animals. The electrocardiographic concomitants of potassium cardiotoxicity in dogs were first clearly described by Winkler, Hoff, and Smith.[8,15] Their work appears to have provided the background for and impetus to analogous observations in man. The essential changes were increased T-wave amplitude, S-T depression, defective intraventricular conduction, and P-wave disappearance. No A-V block occurred. Prolongation of the P-R interval was recorded in hyperpotassemic cats studied by Chamberlain and associates,[3] and in potassium intoxication in man.[6,10] The abnormal S-T elevations noted in the present patient do not correspond to the hyperpotassemic S-T depressions observed in dogs and in man. The cause of the deep Q wave in Lead CF_2 is obscure.

Finch and Marchand and their co-workers[5,6,12] reported six cases of potassium cardiotoxicity. Tall peaked T waves, P-wave absence, S-T depression, decrease in the ratio of R to S, and delayed intraventricular conduction were the chief electrocardiographic findings. In one of their patients[5] ventricular fibrillation, eventuating in asystole, was recorded terminally. Ventricular fibrillation was not observed in dogs subjected to continuous, slow intravenous infusion of potassium chloride[15] but was observed in an anuric dog to which potassium chloride was administered by duodenal intubation.[17]

Keith and associates[10] found P-wave changes (widening and disappearance) and prolongation of the P-R interval in their cases of hyperpotassemia and uremia. Delayed intraventricular conduction and a tendency to peakedness of the T waves were also observed. Katz[9] recorded electrocardiograms of two uremic patients; in these tracings, peaked T waves were evident in the limb leads and CF leads. No serum potassium levels were mentioned. Govan and Weiseth[7] recorded limb lead aberrations suggestive of hyperpotassemia in conjunction with a serum potassium of 12.27 mM per liter (48 mg. per 100 c.c.).

The electrocardiographic alterations observed in the present case are comparable to those observed in anuric dogs.[8] The anuric animals evidenced levels of elevation of serum potassium concentration, sequential electrocardiographic changes, and a mode of death precisely comparable to normal dogs subjected to continuous intravenous potassium infusion.[15] In the latter animals, an increase in amplitude and decrease in duration of the T wave occurred at serum potassium levels of 5 to 8 mM per liter (19.5 to 31.3 mg. per 100 c.c.). Depression of S-T at 8 to 10 mM per liter (31.3 to 39.1 mg. per 100 c.c.), intraventricular conduction delay at 10 mM per liter, P-wave disappearance at 9 to 11 mM per liter (35.2 to 43.0 mg. per 100 c.c.), and cardiac arrest at 14 to 16 mM per liter (54.7 to 62.5 mg. per 100 c.c.) constituted the subsequent electrocardiographic evidence of increasing serum potassium concentration.

Repeated serum potassium determinations in our case disclosed consistently elevated potassium levels. The magnitude of fluctuation of serum potassium appears to be positively correlated with fluctuations in degree of corresponding electrocardiographic change. In this connection, the importance of securing blood for potassium determination at the same time as the electrocardiogram is taken is evident. Further studies of potassium cardiotoxicity in man may determine possible threshold serum potassium levels at which various electrocardiographic abnormalities appear. The critical lethal level in man had been postulated at 10.0 or 10.5 mM per liter of serum.[6] Survival, despite serum potassium levels of 12.27 mM per liter[7] and 14.1 mM per liter,[14] has been reported. The fact that other electrocardiographic manifestations in the uremic state (for example, those associated with hypertension, coronary insufficiency, and pericarditis) may result in a somewhat varying electrocardiographic reflection of potassium intoxication from case to case may account for variations to be found in the various case reports.

Persistent anuria or oliguria are presumably the cardinal prerequisites for the development of hyperpotassemia.[8] Previous case reports[5,7,10,12] support this hypothesis. The present patient (Chart I) likewise appears to confirm this theory. That potassium intoxication may occur without marked reduction of urine flow is suggested by the following: One of the patients observed by Hoff and associates[8] was anuric for two or three days preceding death. The serum potassium was 6.5 mM per liter two hours prior to death, and there was no electrocardiographic evidence of potassium intoxication. Some of the reported cases[5,6,10,12] and the present case manifested hyperpotassemia and related electrocardiographic changes in the absence of complete or nearly complete urinary suppression. Of the factors other than oliguric potassium retention which may be involved in potassium intoxication, the following may be important: (1) a shift of nonplasma potassium into the plasma; (2) renal dysfunction, not directly related to urinary suppression, involving defective conservation and/or excretion of electrolytes; and (3) adrenocortical factors. If the hypochloremia present in our patient (Chart I) indicated concomitant hyponatremia, an influx of potassium from the intracellular fluid may have occurred. This shift of potassium to the extracellular compartment, in association with excess sodium loss

via the kidney and/or defective potassium excretion, may explain the abnormally high serum potassium levels noted in the present case.

Clinically, in association with potassium intoxication, flaccid paraplegia and quadriplegia of sudden onset were observed.[5,6] These disturbances were not observed in other reported cases[7,10,12] nor in the present instance. That flaccid paralysis of the family-periodic type may occur in a nonoliguric form of renal insufficiency in a hypopotassemic phase has been suspected.[1] Therapeutic approaches in man and in animals to the problem of potassium intoxication have included the administration of sodium chloride,[6] insulin,[2] hypertonic glucose,[2,7] calcium,[7,12,16,20] and adrenocortical compounds.[4,6,18] Whether hypocalcemia and/or hyponatremia occurring in the course of renal insufficiency may enhance the deleterious effects of elevated serum potassium levels is unknown.[6]

In conclusion, it may be well to point out again that the administration of potassium salts to patients in renal insufficiency may be frought with danger. This practice may be particularly deleterious in the presence of impending or actual urinary suppression. Keith and associates[11] observed increases of 6.3 and 10.4 mg. per 100 c.c. in the serum potassium levels following ingestion of 5.0 Gm. of potassium bicarbonate by each of two patients with renal insufficiency. Some of the reported instances of potassium intoxication have involved administration of potassium salts for therapeutic purposes.[5,7,10] On the other hand, as demonstrated by Winkler and associates,[17] there are many factors which tend to preclude dangerous serum potassium levels following oral administration of potassium salts to patients in states of frank renal insufficiency.

SUMMARY

1. Data are given on a patient who manifested uremia, hyperpotassemia, and electrocardiographic changes consistent with potassium cardiotoxicity.

2. Huge, peaked T waves of relatively brief duration, conduction disturbances, and P-wave changes were the salient abnormalities.

3. A brief discussion of factors which may be involved in the genesis of potassium intoxication was undertaken.

The advice and criticism of Dr. R. V. Ebert are gratefully acknowledged.

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Abstracts and Reviews

Selected Abstracts

Gorham, L. W., Lester, D. E., Wolf, A. V., and Shultz, H. H.: The Relative Importance of Dietary Sodium Chloride and Water Intake in Cardiac Edema. Ann. Int. Med. 27:575 (Oct.), 1947.

Thirty patients with edema of congestive heart failure were investigated. Twenty-two of these were maintained on a low salt diet of less than 1.0 Gm. of sodium chloride in twenty-four hours. Eight patients were allowed 3.0 Gm. of sodium chloride in twenty-four hours. The fluid intake was frequently altered. Daily fluid intake varied from 1,000 c.c. to 7,500 c.c. in different patients on different days. When encouraged to do so, most patients took an average of 3,000 c.c. daily. Some were on fluids restricted below 1,500 c.c. throughout the first week of treatment, others were forced to over 4,000 c.c., while still others were restricted during the first three days of treatment and forced during the subsequent four days, and vice versa. These varying intakes were employed during the first seven days because the maximum excretion of sodium occurred during the first week of the regimen. After the first week, fluids were allowed as desired. With a few exceptions, all patients were fully digitalized at least thirty-six hours before the regimen was started. Very satisfactory clinical improvement was noted in the majority of the twenty-two patients treated with less than 1.0 Gm. of sodium chloride in twenty-four hours. Seventeen cases showed a satisfactory clearing of edema. In five cases, maintained four to fifteen days on the less than 1.0 Gm. of sodium chloride in twenty-four hours, there was no apparent clinical improvement. Loss of edema was achieved without recourse to mercurial diuretics. Clinical evidences of edema disappeared usually within one week. No adverse effects were noted which could be directly attributed to the ingestion of extra water. However, five of the patients with chronic edema of long standing responded very poorly to the diet and ingestion of water alone. In these cases, the authors believe that the use of mercurial diuretics was mandatory.

In general, the clinical responses of all the patients seemed to depend on their ability to excrete sodium. Where the sodium chloride excretion was very low, the patients responded poorly. Although forcing fluids caused some increase in sodium and water loss, the slightly negative sodium balance was seemingly not enough to affect the clinical course. However, in none was there any adverse effect from the ingestion of copious amounts of water when the diet was kept low in sodium.

This regimen is not considered by the authors to be a substitute for mercurial diuretics, especially in the more refractory cases. The relative sodium loss of three to five days on the regimen for the average patient was only the equivalent of that obtained by 1.0 c.c. of Salyrgan. Nevertheless, they consider that the low sodium diet and moderate intake of water (3,000 c.c. daily) appear to be most valuable adjuncts to digitalis and the mercurial diuretics in the treatment of cardiac failure.

WENDKOS.

Reader, G. G., Romeo, B. J., Webster, B., and McDermott, W.: The Prognosis of Syphilitic Aortic Insufficiency. Ann. Int. Med. 27:584 (Oct.), 1947.

In 1942, the authors had under their direct observation ninety-one patients suffering from syphilitic aortic insufficiency. In forty-seven of this number, supplementary studies, such as

circulation time, venous pressure, vital capacity, and teleroentgenogram of the chest, were made. Thirty of this carefully studied group of patients are known to be still alive, but only twenty-seven of the original group of forty-seven were available for comparative study and symptomatic appraisal. Of this number, sixteen have remained asymptomatic, three admitted to mild symptoms of cardiac failure on careful questioning, and eight presented frank evidences of myocardial insufficiency such as exertional and/or paroxysmal nocturnal dyspnea. Of the sixteen who are asymptomatic, ten are 60 years of age or older, while the remaining six range in age from 43 to 59 years. Most of these asymptomatic patients are still working. Of the eight who complained of dyspnea, two are 60 and 71 years of age, respectively, whereas the remainder range in age from 35 to 57 years. In the symptomatic and asymptomatic groups, aortic insufficiency has been known to be present for approximately the same length of time, that is, for five to twelve years, with an average of 7.6 years. Compensation has been restored by treatment with digitalis in nine of the symptomatic group. The symptomatic phase in this group has varied from two to fourteen years, with an average of 5.6 years. Nine of the total number of surviving patients had been in congestive heart failure three to nine years previously and had responded very well to digitalis. All the patients included in this study had received continuous antisyphilitic therapy with bismuth and arsenicals for approximately four years.

Abnormal widening of the aorta did not appear to be a factor affecting the prognosis, whereas a low diastolic blood pressure was recorded in only two of those who have survived the five year follow-up period. The intensity of the murmur did not seem to bear any relationship to the ultimate outcome, since a loud diastolic murmur was frequently heard in those who had remained asymptomatic while the murmur was soft in many who had always been symptomatic. It is the conclusion of the authors that of all the tests available, the circulation time and the diastolic blood pressure probably offer the best index of prognosis in syphilitic aortic insufficiency.

WENDKOS.

Melvin, J. P., Jr.: Post-partal Heart Disease. Ann. Int. Med. **27**:596 (Oct.), 1947.

Four female Negro patients, two of whom were 21 years of age and the other two 31 and 32 years of age, developed congestive heart failure during the postpartum interval, shortly after the uncomplicated delivery of their respective infants. There was no history of antecedent rheumatic infection nor syphilis in the entire group and serologic tests were uniformly negative. In all cases, the diet appeared to be adequate throughout pregnancy and there were no stigmata of nutritional deficiency which could be detected in the physical examination. Temporary elevations of the diastolic blood pressure were noted in all cases during the phase of cardiac decompensation. Ectopic rhythms were not present. The only adventitious cardiac sounds consisted of transient systolic murmurs and protodiastolic gallop rhythms. Teleroentgenograms of the chest in all instances revealed definite cardiac enlargement, which disappeared following restoration of cardiac compensation. Low-grade fever was present in one case but the cause for the pyrexia was never established in spite of repeated blood cultures. In all four instances, uneventful recovery from the congestive heart failure followed bed rest, diuresis, and digitalis, whereas no benefit seemed to result from the administration of concentrates of vitamin B complex. The author considers that the clinical findings in these cases confirm previous concepts that reversible disease of the heart, directly incidental to pregnancy, may be a definite clinical entity.

WENDKOS.

Underdahl, L. O., and Smith, L. L.: Coronary Artery Disease in Women Under the Age of Forty. Proc. Staff Meet., Mayo Clin. **22**:479 (Oct. 15), 1947.

The authors studied the records of 95,000 women under the age of 40 years who were seen during the eleven-year period, 1935 through 1945, and found a total of twenty-seven patients in whom there was no reasonable doubt of the diagnosis of coronary disease. The ratio is, therefore, one case of coronary artery disease in every 3,500 patients. This series included cases of coronary sclerosis with angina pectoris and coronary sclerosis with myocardial infarction. The criteria for diagnosis are the same for coronary disease in women under the age of 40 years as in any other group. In this series, there was only one patient who had diabetes.

There were seven patients who had definite myocardial infarction and two others who had questionable infarction. Of these seven patients, two died suddenly while under observation in the hospital and another died five weeks after returning home. The remaining twenty patients had coronary sclerosis with angina pectoris. Two of these had a history which suggested previous myocardial infarctions, but the diagnosis could not be proved.

Of the twenty-seven patients, only one was under the age of 35 years. Thirteen of the twenty-seven patients had varying degrees of obesity. Seventeen of the patients (63 per cent) had varying degrees of hypertension. Of the five patients who were of normal weight and had infarction, four had hypertension; the fifth had neither obesity, hypertension, nor hyperlipemia. Of fourteen patients who had blood fat determinations, eight showed elevation and six had normal values.

The results of this study confirm previous impressions that coronary disease in women under the age of 40 years is very rare.

BELLET.

Lewis, L. A., and Page I. H.: Changes in the Plasma Protein Pattern (Tiselius Electrophoretic Technique) of Patients With Hypertension and Dogs With Experimental Renal Hypertension. J. Exper. Med. **86**:185 (Aug.), 1947.

Employing the Tiselius electrophoretic technique, the author studied the plasma protein pattern of ten patients with essential hypertension, sixteen patients with malignant hypertension, that of six dogs before and after the development of hypertension induced by wrapping both kidneys in silk, and that of three dogs in which the spleen was wrapped in silk. The sixteen patients with malignant hypertension were classified according to the severity of the disease into mild, moderate, and severe cases. The proteins studied were albumin, alpha, beta, and gamma globulin, and fibrinogen.

The plasma portein pattern of the patients with uncomplicated essential hypertension showed only slight variations from the normal. In those with severe malignant hypertension, the fibrinogen and beta globulin were usually elevated and the albumin increased. These changes were less marked in less severe cases of malignant hypertension. In the dogs with experimental hypertension, the gamma globulin level was greatly elevated, and in one dog with the malignant hypertension syndrome, beta globulin and fibrinogen were also increased. It is concluded that elevation of beta globulin seems in some manner to be associated with the occurrence of severe vascular disease.

MERANZE.

Miale, J. B.: Characteristic Urinary Findings in Visceral Angiitis. (Periarteritis Nodosa, Lupus Erythematosus). Am. J. Clin. Path. **17**:820 (Oct.), 1947.

Urinary findings in three cases of visceral angiitis (periarteritis nodosa, lupus erythematosus) are listed. These consist of erythrocytes and erythrocytic casts, waxy casts, fatty casts, broad casts, and "oval fat bodies." This urinary picture has been described so seldom in acute glomerulonephritis that it is considered presumptive evidence of the presence of visceral angiitis in the acute phases. These findings disappear with remission of the disease.

MERANZE.

Jones, J. C.: Complications of the Surgery of Patent Ductus Arteriosus. J. Thoracic Surg. **16**:305 (Aug.), 1947.

Jones discusses the types of morbidity and mortality incident to the operative management of sixty-one consecutive patients with patent ductus arteriosus. In none of the patients was there a preoperative bacterial endarteritis. In fifty-three patients the ductus was ligated and in eight it was completely divided and sutured. Two deaths occurred. One occurred during operation when a massive hemorrhage from the ductus necessitated division and suture; cardiac arrest developed and resuscitation was unsuccessful. The second death occurred forty-eight days

following ligation; autopsy showed a re-established fistula around the ductal ligatures between the pulmonary artery and the aorta. In addition, an aneurysm of the ductus was found. During the two weeks before death a blood stream infection with *Staphylococcus aureus* associated with a high fever developed. Vegetations were found on the walls of the pulmonary artery and aorta.

Of the fifty-nine living patients, ten have clinical evidence of either recurrence of the fistula or inadequate obliteration of the ductus. All but one of this group, however, are well.

Two patients developed aortobronchial fistulas with intermittent hemoptysis, necessitating operative intervention in one of them. The two umbilical tapes had eroded into the aorta and a small bronchus of the left upper lobe. The opening into the aorta was sutured and a complete recovery ensued. Other complications included atelectasis, pneumonia, and two cases of empyema.

LORD.

Gross, R. E.: Complete Division for the Patent Ductus Arteriosus. J. Thoracic Surg. **16**:314 (Aug.), 1947.

Gross supports his contention that the patent ductus should be divided and sutured in every case subjected to operation by the facts that there have been only four deaths in 180 consecutive cases, whereas in forty-three patients treated by some form of ligation, there were three deaths and a recurrence or continuation of the fistula in approximately eight cases. Since complete division in the author's hands carried a mortality no higher, but rather lower, than ligature of the ductus, and since complete division cannot be followed by recurrence, he has employed it routinely in all cases, infected as well as uninfected, for the past three years.

The technique is illustrated and described in detail. An anterior approach through the left chest with reflection of the breast cephalad is employed. Careful and complete dissection of the areolar and fibrous tissue from the ductus and adjacent pulmonary artery and aorta is essential. The ductus is divided between four clamps and after removal of the two innermost clamps, each end is sutured with 00000 Deknatel silk. There has been no instance of immediate or delayed hemorrhage or aneurysm.

LORD.

Conant, J. S., and Kurland, L. T.: Pulmonary Tuberculosis Associated With Anomalous Common Left Pulmonary Vein Entering the Left Innominate Vein. J. Thoracic Surg. **16**:422 (Aug.), 1947.

The authors report the occurrence of an anomaly of the left common pulmonary vein in a 37-year-old Negro. Bilateral pulmonary tuberculosis was discovered four years before his death in 1946. The lesions in the right lung responded well to rest and other measures, but a cavity in the left upper lobe enlarged progressively from 3 cm. to 10 cm. in diameter during the four-year observation period. Death followed rapidly the development of a right pleural effusion.

Necropsy showed that the left auricle received only one pulmonary vein, that from the right side, which divided as it passed through the pericardium. The circulation of the right lung was normal. Further exploration of the pulmonary circulation showed a common left pulmonary vein emptying into the left innominate and picking up a tributary from what appeared to be the left hemiazygous above the level of the left pulmonary artery.

It would appear that by itself recirculation of aerated blood from one lung into another, by a shunt involving half the pulmonary bed, still provides an adequate pulmonary reserve. In the case reported, the arterial blood received all its oxygen from the right lung. The addition of pulmonary disease to the picture suggests in this instance that the integrity of the right lung was more important than that of the left. Obstruction to the flow of blood through the right lung, which was directly concerned with maintaining the oxygenation of the systemic circuit, had a more serious effect than involvement of the left lung. Up to the time the patient suffered his terminal episode, the tuberculosis was more extensive on the left side. When spread to the right lung occurred and was associated with a right-sided effusion, the supply of oxygen and blood to the systemic circuit then became limited.

LORD.

Corcoran, D. B., and Coleman, F. P.: Anomaly of Aorta Simulating Mediastinal Tumor. J. Thoracic Surg. **16**:427 (Aug.), 1947.

Corcoran and Coleman point out that many mediastinal tumors are asymptomatic and are discovered only during routine roentgenologic examination. Following discovery of such a lesion, an accurate differential diagnosis may be difficult, although Coleman was able to determine the cellular nature of the pathology preoperatively in eleven of nineteen cases.

Aneurysms and anomalies of the thoracic aorta are sometimes mistaken for mediastinal tumors and the authors report such a case. A 58-year-old man was found by roentgenographic examination of the chest to have a dense mass in the posterior mediastinum between the levels of the seventh and tenth ribs. It bulged laterally into the left hemithorax and displaced the barium-filled esophagus anteriorly. At operation a markedly elongated descending thoracic aorta was found which had a horseshoe-shaped curve. The authors discuss the possible embryologic orgins of such an anomaly.

LORD.

Jampolis, R. W., Jenkins, H. P., Newman, M. M., and Nardi, G. L.: Control of Hemorrhage From the Cardiac Auricles by the Gelatin Sponge, An Experimental Study. **Surgery 22**:198 (Aug.), 1947.

In Elkin's series, in 1944, the mortality rate in wounds of the four cardiac chambers, the aorta, and the pulmonary artery was 22 per cent. In three cases of injuries to the auricles, there was one death, a mortality rate of 33 per cent. In a series of forty-two patients with wounds of the heart reported by Griswold and Maguire, the wounds in four were in the auricles, and three of these patients died. The present authors point out that there are a number of factors which are responsible for the high mortality rate in wounds of the auricles. First, the left auricle is difficult to expose; second, the walls are thin and friable, making the hemorrhage large and rapid, as a rule, and making suturing difficult.

In a group of eighteen dogs, the tip of the auricular appendage was removed and a knife was thrust into the auricular wall at the base of the appendage in order to produce severe hemorrhage. A gelatin sponge was applied to the defect and held in place for ten minutes. It is compressed, used dry, and Cilkloid is employed to prevent the sponge from adhering to the surgeon's glove. There were no instances of secondary hemorrhage. At autopsy the sponge was adherent to the epicardium and was absorbed in from five to eight weeks. The authors present their experiments as a technique which might have "value in clinical surgery as an aid in controlling hemorrhage in stab wounds or bullet wounds of the auricles, in injury of the auricle in the course of pericardiectomy, and in operative procedures on cardiac valves."

LORD.

McSwain, B., and Spencer, F. C.: Carotid Body Tumor in Association With Carotid Sinus Syndrome. Surgery **22**:222 (Aug.), 1947.

Although 275 cases of carotid body tumors have been reported in the literature, only six unequivocable cases of the carotid sinus syndrome have been recorded in association with carotid body tumors. The authors add two new cases. In one patient, a boy, 15 years of age, there was a 2-year history of fainting spells and a mass in the neck of one year's duration. Pressure on the mass, which was located in the left side of the neck just below and posterior to the angle of the mandible, caused cardiac slowing, an imperceptible blood pressure, and syncope. Following release of pressure, the blood pressure and pulse rate returned to normal in one minute. At operation it was necessary to resect portions of the common, internal, and external carotid arteries in order to extirpate the tumor. On microscopic study it was found to have invaded the coats of the common carotid artery. The cellular elements were typical of a benign adenoma or tumor of the carotid body. The patient made an uneventful recovery and has remained free from further syncopal attacks. Two and one-half years after operation, a 2.0 x 2.0 x 1.0 cm. mass was found in the region of the bifurcation of the right common carotid artery. No symptoms were caused by pressure upon the mass. Excision of the tumor has been advised.

The second case was a 28 year-old woman who had had many attacks of syncope associated with turning of the head over a period of eight years. A mass in the left side of her neck had been present for three years. Syncopal attacks ceased three years before admission and were replaced by sensations of faintness. For one month, the patient had noted atrophy of the left side of the tongue. At operation the common, external, and internal carotid arteries were ligated and the mass removed. The internal carotid artery was found to be thrombosed. Microscopically, the specimen was typical of a carotid body adenoma. Postoperatively, a transient right-sided hemiplegia occurred but disappeared completely in forty-eight hours.

In both operations it was necessary to sacrifice several nerves, resulting in left vocal cord paralysis in both patients and a Horner's syndrome in the first case.

The authors discuss the possible theories of the spontaneous disappearance of the carotid sinus syndrome in the second case of carotid body tumor and suggest that thrombosis of the internal carotid artery may have abolished the cerebral type of reflex. They favor, however, the concept that the tumor may have destroyed the afferent nerve connection from the carotid sinus, thereby breaking the reflex arc.

LORD.

Simeone, F. A., and Sarnoff, S. J.: The Effect of Dibenamine on the Autonomic Stimulation. Surgery **22**:391 (Aug.), 1947.

An experimental study was performed on cats to determine whether Dibenamine blocks the effects of sympathetic nerve excitation, as well as the action of epinephrine. The nictitating membrane, disconnected from the central nervous system by severing the cervical sympathetic trunk, was utilized as a test organ. The membrane was previously sensitized by postganglionic denervation.

The data demonstrated that Dibenamine blocks the positive action of epinephrine, at the same time unmasking its negative effects. The action of sympathin E is also blocked. However, the blocking effect is not as great in the case of the changes produced by sympathetic nerve stimulation. Dibenamine does not inhibit at all the cardioacceleration following excitation of the cardiac nerve and only diminishes, but does not abolish, the contraction of the nictitating membrane in response to stimulation of the cervical sympathetic nerves.

Since the effect of Dibenamine is not immediate, the authors suggested that the action of the drug is not a direct one upon epinephine or sympathin, but rather that it effects some substance between the mediator and the contractile mechanism or possibly the contractile mechanism itself. The latter theory appears to fit the facts best.

ABRAMSON.

Loewe, L.: Anticoagulation Therapy With Heparin/Pitkin Menstruum in Thromboembolic Disease. Am. J. Med. **3**:447 (Oct.), 1947.

This is one of a series of seminars on thromboembolism. The author's experience with the use of heparin/Pitkin menstruum in a series of more than 400 patients receiving several thousand subcutaneous deposits is the basis of the report. The functional pathology of intravascular clotting is reviewed and the disadvantages and limitations of surgical interruption of veins and the use of Dicumarol in thrombophlebitis and/or phlebothrombosis is discussed.

The author feels that heparin is uniquely applicable in thromboembolic disease and that the heparin/Pitkin menstruum circumvents previous disadvantages of the substance. Composition, dosage plan, method of administration, clinical use, and method of following the patient's clinical course are discussed in detail.

Local pain, swelling, and tenderness caused by the earlier preparations do not occur with the present preparations. Suspension of heparin activity may be obtained with small transfusions of whole blood. It is felt that the substance is safe, simple, practical, and effective for anticoagulation therapy.

An analysis of the clinical results in 251 patients representing all forms of venous thromboembolic disease revealed good results. There were five fatalities. Loewe believes that there is a parallelism between thrombus mass and heparin requirements. In uncomplicated phlebothrom-

bosis, heparinization need be continued only for seven to ten days, while cases complicated by pulmonary infarction require an additional seven to ten days of heparinization. The liberal use of papaverine is recommended.

The problem of prophylaxis in the field of thromboembolism, as it pertains to heparin/Pitkin menstruum, is discussed, as well as the treatment of arterial thromboembolic disease (peripheral vascular disease, cerebral thrombosis, and coronary artery thrombosis).

WOODS.

Boger, W. P., Kay, C. F., Eisman, S. H., and Yeoman, E. E.: Caronamide, a Compound That Inhibits Penicillin Excretion by the Renal Tubules, Applied to the Treatment of Subacute Bacterial Endocarditis. Am. J. M. Sc. 214:493 (Nov.), 1947.

It is now established that approximately 80 per cent of the loss of penicillin from the body is by way of the renal tubules. Therefore, an agent capable of inhibiting tubular excretion might be expected to enhance the levels of penicillin in the plasma. These effects have been observed to follow the administration of Diodrast, para-aminohippuric acid, and benzoic acid. Diodrast and para-aminohippuric acid have been employed in the treatment of subacute bacterial endocarditis, but the necessity of administering large amounts of either substance by constant intravenous infusion has limited their usefulness.

A new compound, Caronamide, has been described as being effective in elevating the plasma concentrations of penicillin. It has been hypothesized that the physiologic and reversible inhibition of the penicillin transport mechanism under these circumstances is due to a substrate competition between penicillin which is excreted by the tubules, and Caronamide (4′-carboxy-phenylmethane-sulfonanilide) which is essentially refractory to excretion by the transport mechanism. In preliminary clinical investigations, penicillin plasma concentrations were enhanced from three to seven fold by the oral administration of Caronamide, and no serious toxic manifestations were observed. Accordingly, the treatment of a case of subacute bacterial endocarditis due to a strain of *Streptococcus viridans* resistant to penicillin and streptomycin was considered to be justified.

The patient was a 51-year-old woman who had suffered relapse following each of two courses of penicillin therapy. The sensitivity of the organism to penicillin had originally been 0.03 unit per cubic centimeter, but after the second course it was 0.5 unit per cubic centimeter. Two courses of streptomycin were then administered, but cure was not effected and there was a 20,000-fold increase in the resistance of the organism to this antibiotic. Following the failures with streptomycin, penicillin was again administered, but this time in association with oral Caronamide in dosage ranging from 12 to 24 Gm. per day. It was possible by this combination to elevate the plasma concentration to the remarkable height of from 30 to 60 units of penicillin per cubic centimeter. On the ninth day of this course, the blood cultures became negative and remained so thereafter. Another combined course was given later for prophylactic purposes when the patient had a tooth extracted. No reactivation of the disease occurred. It was estimated that the blood levels which were obtained in this case with combined treatment could only have been obtained with penicillin alone had 10,000,000 units daily been administered.

DURANT.

Minkowski, W. L.: The Coronary Arteries of Infants. Am. J. M. Sc. 214:623 (Dec.), 1947.

Considering the enormous volume of literature devoted to the coronary arteries, the dearth of attention given these vessels in the newborn, infants, and children is rather surprising. A few investigators have included the coronary arteries of young people in overall surveys of age changes occurring in these vessels; none have studied infantile coronary arteries in numbers adequate for statistical analysis. To meet this need, there are reported the histologic studies on the coronary arteries of 204 infants, most of whom died at birth or soon afterward. The causes of death were, in general, limited to birth injuries and/or asphyxia, inflammatory processes, and a small number of miscellaneous diseases unrelated to either of the former groups. Sections about 5.0 mm. thick were taken from each of the three major coronary arteries at a distance of 0.5 to 1.0 cm. from their origins. A special magnification technique was used for the measurement of the areas of the intima and media.

It was found that 60 per cent of 122 male subjects and 51 per cent of eighty-two female subjects revealed a musculoelastic and/or an elastic hyperplastic layer in one or more of their coronary arteries. It may, therefore, be concluded that coronary intimal thickening occurs in a large number of newborn infants and children dying of various causes. In a group of fifty-one boys and twenty-five girls less than one day old who died of birth trauma and/or asphyxia, the mean difference between the male and female intima-media rates of 2.6 times the probable error of the means was obtained. This is considered to be a highly suggestive difference. The validity of this difference and of that in Dock's material must be determined by examination of greater numbers of hearts.

The role played by infection was also of great interest in this study. Bronchopneumonia was a very common infection in the series of cases studied. For the entire group, and particularly for the group more than one month old, the differences in means for coronary intimal thickening between the group with infection and the group without infection were clearly significant.

The meaning of the intimal thickenings found in this study, particularly as it concerns the subsequent development of coronary arteriosclerosis, remains to be clarified.

DURANT.

Barany, F.: Peripheral Blood-Flow in Rabbits With Experimental Hypertension. Acta med. Scandinav. **127**:376 (No. V), 1947.

The author repeated the experiments of Kapp, Friedland, and Landis (1941) which had shown that the ear temperature of rabbits with nephrogenic hypertension remained the same when the animals were warmed to 40° centigrade. It had been inferred that an increase in vascular resistance occurred in the skin directly proportional to the blood pressure increase. Because he felt the rabbit's ear was primarily a heat radiator and therefore its temperature a poor index of cutaneous blood flow, the author repeated the experiments, measuring not only the temperature of the ear, but also that of the forepaw in warmed rabbits with hypertension produced by the Page cellophane technique.

There was no evidence of vasoconstriction associated with the increased pressure, as compared with controls, when the forepaw was used. The ear temperature remained constant just as it did in the 1941 experiments.

Since patients with renal hypertension do not have an increase in skin blood flow and, therefore, are assumed to have vasoconstriction in the cutaneous bed, there appears to the author to be an important difference between human and rabbit renal hypertension; there is either a different etiological agent or a different response to the same agent.

SAYEN.

Oster, J.: Arterial Hypertension in a Child, Cured by Nephrectomy. Acta med. Scandinav. **128**:42 (No. I), 1947.

After reviewing the unilateral renal affections associated with hypertension, the author reports the case of a 7-year-old boy with intermittent leftsided hydronephrosis ascribed to pressure of an aberrant artery on the ureter. The blood pressure was not determined preoperatively. A darning-needle-sized aberrant artery to the lower of the kidney pole was found and ligated. After one month, headache, nausea, and vomiting appeared from time to time, and five months after operation, the child developed hypertensive encephalopathy with a blood pressure of 200/170. After the acute encephalopathic bout subsided, the blood pressure was 180/130 and the blood urea nitrogen 36 mg. per cent.

Left nephrectomy was performed and pathologic examination of the kidney revealed changes in the lower pole thought to be due to ischemia, in addition to slight hydronephrosis throughout the organ. The blood pressure fell to normal and fourteen months later was 90/60, the child remaining well. Although there was not entirely convincing proof in this case of a causal relation between ligation of an aberrant renal vessel and hypertension (the duration of the hypertension being uncertain), the author points out the possible danger of such ligations, which, he believes, is not sufficiently realized.

SAYEN.

Peters, J. T.: The Necessity and Possibility of Giving Detoxified Large Oral Doses of Salicylates in the Treatment of Rheumatic Fever in Order to Prevent or Cure the Inflammatory Stage of Carditis. Acta med. Scandinav. **128:**51 (No. I), 1947.

On the basis of "numerous" cases treated since 1929, it is asserted that the dosage of salicylate used in active rheumatic fever is usually insufficient, and that remarkable results can be obtained if blood levels of 35 to 70 mg. per cent are reached. This cannot be accomplished safely with intravenous administration or the usual methods of oral administration. However, if sodium bicarbonate be given in solution in a ratio of 2.0 Gm. for every gram of sodium salicylate, it is possible to give 15 Gm. of salicylate orally each twenty-four hours with relative impunity. The author's formula consists of sodium salicylate, 30 Gm.; sodium bicarbonate, 60 Gm.; and peppermint water, 300 c.c., made up to 1 liter with cold distilled water. Fifty cubic centimeters of this solution are given ten times a day, the dosage being proportionately reduced for children. The importance of administering the salicylate in solution and in not heating the solution while preparing it (to prevent formation of sodium carbonate) is stressed. Neither alkalosis, nor respiratory stimulation, nor vomiting was seen when salicylate was administered in this form and in this dosage. Continuance of therapy till all evidences of activity subsided was important. The sedimentation rate became normal rather early and was not the best guide. A marked decrease in the frequency and severity of carditis is claimed.

SAYEN.

Adler, E., and Lyon, E.: Cardiac Disorders Associated With Infectious Hepatitis. Cardiologia **11:**111, Fasc. 3, 1947.

Seven per cent of a large number of cases of infectious hepatitis with icterus had cardiovascular symptoms and signs. Eight cases are reported and their electrocardiograms shown. The symptoms occurred during the infection, immediately after the acute phase, and after variable intervals following the infection. The subjective complaints were palpitation, dyspnea, pressure sensation in the chest, anginoid pain with occasional radiation into the left arm, fatigue, weakness, and occasional arrhythmias. The ages varied from 20 to 40 years and all were previously healthy. Marked variations in heart size or abnormal auscultatory phenomena were absent.

All cases showed electrocardiographic changes considered to be characteristic of myocarditis. In some cases a return to normal was observed. Changes in A-V conduction, in the form and displacement of the S-T segment at rest and after exercise, and flattening or inversion of the T waves were observed. In addition, sinus arrhythmias and auricular or ventricular premature contractions were noted. In almost all cases the duration of the Q-T segment was prolonged. This is considered to be toxic in origin. In several cases, excessively high T waves were found.

LENEL.

Hedinger, C.: Contusion of the Heart With Late Rupture of the Left Ventricle. Cardiologia **12:** Fasc. 1/2, 1947.

A 53-year-old soldier was kicked in the chest by a horse. Following this episode, he was hospitalized for three days because of severe dyspnea. After discharge he was unable to perform his usual duties and three days later he was again hospitalized. A pericardial friction rub was heard over the precordium. The pulse rate was 120; blood pressure, 120/100; and white blood cell count, 19,200, with 82 per cent polymorphonuclear leucocytes. Fluoroscopy showed enlargement of the heart and pulmonary congestion. The patient died suddenly on the ninth day after the accident.

Autopsy showed a fracture of the sternum at the level of the fourth rib and fracture of the cartilages of two ribs. Examination of the heart revealed a tear of the lateral leaflet of the tricuspid valve; rupture of the descending branch of the left coronary artery near its origin from the aorta, with formation of a dissecting aneurysm and a recent thrombosis of this artery; a very large recent infarct of the left ventricle with mural thrombosis and pericarditis; and rupture of the left ventricle in the region of the infarct with hemopericardium.

The author advocates a longer period of observation after severe trauma to the chest.

LENEL.

Mahaim, I.: New Concepts Concerning the Treatment of Mitral Stenosis. Cardiologia **12:** Fasc. 1/2, 1947.

Mitral stenosis is not always due to scarring of the mitral valve but may be caused by a myxomatous polyp originating in the left atrium and protruding through the mitral orifice. Such polyps may cause arterial myxomatous emboli which can be identified as such after surgical removal. Such polyps are a constant threat to the life of the patient.

The diagnosis can be made by the following suggestive signs and symptoms: The sudden appearance of mitral stenosis in a subject with a negative cardiac history and the sudden appearance of peripheral signs of marked decrease in cardiac output and peripheral embolism. Angiocardiography may reveal the left atrium to have a lacunar appearance.

The author suggests that mitral stenosis due to a polyp and also mitral stenosis due to scarring should be treated surgically by the production of an artificial interauricular septal defect. This recommendation is supported by the fact that patients with mitral stenosis and an associated interauricular septal defect show no evidence of pulmonary congestion, and survive longer than patients with mitral stenosis alone.

LENEL.

De la Barreda, P., Diaz, C. J., and de Molina, A. F.: Neurochemical Regulation of Arterial Pressure (the Endocrine Function of Arteries). Rev. españ de cardiol. **1:**1 (Jan.), 1947.

Stimulation of the central stump of the vagus nerve in dogs produces a temporary hypertensive effect even after removal of the pituitary gland or the adrenals, and after extirpation of liver or kidneys. The effect is blocked by section of the medulla. It is assumed that the effect is mediated to the vascular tree via the spinal cord and the peripheral nerves. The hypertensive response may be obtained in crossed circulation experiments in the nonstimulated animal. It may be observed in a dog that has been transfused with plasma obtained during or shortly after the stimulation of the vagal stump. Plasma from such animals greatly reduces flow of fluids in a Loewen-Trendelenburg preparation of the frog. The hypothetical hypertensive substance is not inhibited by ergotamine. The phenomenon may represent an example of internal secretion of the arterial walls or of certain endothelial structures (glomus bodies), perhaps similar to the assumed production of renin by the juxta glomerular apparatus.

HECHT.

Manning, G. W., and Caudwell, G. C.: The Effect of Demerol, Ergotamine, and Dihydro-Ergotamine on Mortality After Coronary Occlusion in Dogs. Brit. Heart J. **9:**85 (April), 1947.

The authors report the result of Demerol and sympathetic inhibiting agents upon acute coronary occlusion in conscious dogs, using the same experimental conditions and procedures previously described (Manning and associates, 1939). The sympathetic inhibiting drugs used were ergotamine tartrate (Gynergen II, Sandoz) and a new ergot derivative, dihydro-ergotamine (DHE_{45}, Sandoz).

Seventy-two normal dogs were used in these experiments. At operation a loose ligature was placed around the circumflex branch of the left coronary artery close to its origin. Twenty-four hours later, occlusion was effected by traction on the loose ends of the ligature. Three groups of experiments were carried out using Demerol, ergotamine tartrate, and dihydroergotamine. In addition, the coronary arteries of eight dogs were ligated without the use of drugs, as a check on technique and the mortality rate in conscious dogs. Except in the control animals, the drugs were given before the ligation. Electrocardiograms were taken before and after the administration of the drug, before, during, and for thirty minutes after ligation, and then intermittently for some time after the occlusion. An autopsy was performed on all animals that died. "Sudden death," for the purpose of these studies, means death within the first twenty-four hours.

Including the former control series of sixteen dogs reported in a previous study, the mortality for the untreated group was eighteen deaths in twenty-four dogs within the first twenty-four hours, or 75 per cent.

Demerol was given intramuscularly to twelve dogs in doses of 10 mg. per kilogram of body weight, followed by a second injection of 5 or 10 mg. per kilogram intravenously fifteen to twenty-five minutes later. This drug did not afford much protection against cardiac irregularities, tachycardia, and fibrillation following sudden coronary occlusion. The outstanding feature was the rapid onset of ventricular tachycardia, which occurred in eleven experiments and within two to four minutes terminated in fatal ventricular fibrillation in seven of the twelve animals. Only five of the twelve dogs survived the twenty-four-hour period.

Ergotamine tartrate was administered to thirteen dogs. In the first two animals, 0.5 mg. per kilogram of ergotamine tartrate was given intravenously. In view of untoward effects, a dose of 0.25 mg. per kilogram was given to the remaining eleven dogs. Shortly after the intravenous injection of ergotamine tartrate the animals showed marked muscular weakness, most apparent in the limbs. Increased respiration and dyspnea, which in several animals was of an asthmatic nature, were prominent features. Ergotamine tartrate in doses of 0.25 mg. per kilogram was effective in inhibiting the development of ventricular fibrillation and so reduced the "immediate" mortality. A delayed cardiac death, however, occurred twelve to eighteen hours later in 70 per cent of the animals.

Dihydroergotamine (DHE_{45}) was given intravenously, 0.4 mg. per kilogram, to twenty-three animals four to five minutes prior to the occlusion. Although most of the animals appeared slightly unsteady following the occlusion, the general collapse and weakness and toxic appearance that was such a prominent feature in the ergotamine series was not apparent. Clinically, these animals appeared more like the control dogs that survived the immediate effects of the occlusion. Seven of the twenty-three dogs died within the twenty-four-hour period following ligation (30 per cent mortality). Three of these died in ventricular fibrillation within twelve minutes following occlusion (13 per cent mortality). The remaining four died seventeen to nineteen hours after ligation. In comparison with the ergotamine tartrate series, it is apparent that DHE_{45} was not only similar in its protecting action against the ventricular fibrillation mechanism, but also significantly increased the survival rate.

BELLET.

Szekely, P., and Snaith, L.: The Heart in Toxemia of Pregnancy. Brit. Heart J. 9:128. (April), 1947.

This paper is based upon the observations made in nineteen unselected cases of toxemia of pregnancy. The majority of cases were classified as severe, the criteria being subjective symptoms, such as headache, vomiting, and visual disturbance, and objective findings, such as height of blood pressure, edema, albuminuria, and the occurrence of eclamptic convulsions.

In the present series, a total of seven patients (37 per cent) were thought to have significant changes in the heart; two showed clinical changes only, four showed electrocardiographic changes only, and one showed clinical and cardiographic evidence of cardiac involvement. The electrocardiographic changes were indicative of myocardial damage in at least five cases, because they occurred in both standard and chest leads, and persisted for sometime after delivery, so that the alteration in the anatomical position of the heart during pregnancy could be excluded as a causative factor. The changes in the heart appear to be temporary, but their duration varies considerably. The changes may not only persist for some time after delivery, but may become greater in the post-partum period.

The observations of the authors indicate that gross cardiac enlargement is not a feature of pure "toxemic" cardiac lesion, irrespective of the presence or absence of cardiac failure. Only one of the cases showed enlargement of the left ventricle. If gross cardiac enlargement is present, it probably indicates either antecedent hypertension or heart disease which is not "toxemic" in origin. There is nothing to suggest that pericardial effusion is present in toxemia or pregnancy to account for the electrocardiographic changes or the heart failure. Toxemia of pregnancy is an acute vascular disorder; in this respect, it closely resembles acute glomerulonephritis.

Although convincing proof is still lacking of direct damage to the myocardial vessels in toxemia of pregnancy, in the light of the clinical and anatomic findings, the possibility of struc-

tural damage to the small branches of the coronary arteries cannot be excluded with certainty. The true significance of the observations presented in this paper is their demonstration that cardiac involvement is not uncommon in toxemia of pregnancy. The authors believe that some of the cases of acute ante-partum or post-partum cardiac failure of undetermined etiology may be instances of toxemia even if the recognized signs of the latter condition are not convincingly present; and that some of the cases of vascular collapse known as "obstetric shock" may be instances of true toxemia.

BELLET.

Acosta, F. R.: Ayerza's Disease. Rev. cubana de cardiol. **65**:00 (April), 1947.

Three factors must be present in the pathogenesis of Ayerza's disease:

(1) Primary sclerosis of the fine- and middle-sized branches of the pulmonary artery with resulting hypertension of the lesser circulation. (2) Hypertrophy and dilatation of the right ventricle with ultimate right-sided failure. (3) Extensive pulmonary lesions, consisting of fibrosis, emphysema, and bronchitis. These alveolar lesions produce hypoventilation and irregular gaseous exchange which result in decreased oxygen saturation and increased carbon dioxide content of the arterial blood, and thereby produce the intense cyanosis and dyspnea which characterize the disease and give its victims the name of "black cardiacs."

GOLD.

Binet, L., and Burstein, M.: Action of Carbon Dioxide on the Tonus of Peripheral Vessels. Compt. rend. Soc. de biol. **141**:488 (May), 1947.

The circulatory effects of breathing various concentrations of carbon dioxide were studied in the perfused foot of the dog. It was found that hypercapnea caused an intense peripheral vasoconstriction which persisted after section of the four depressor nerves. Hypocapnea was accompanied by an often marked degree of peripheral vasodilatation. The direct action of carbon dioxide on the peripheral vessels appeared to be insignificant.

LAPLACE.

Charlier, R., and Philppot, E.: Hypotension in the Right Ventricle During Occlusion of the Carotid Arteries. Compt. rend. Soc. de biol. **141**:531 (May), 1947.

Observations were made of the effect produced by occlusion of the common carotid arteries on the pressure in the right ventricle. The experiments were performed on anesthetized dogs. A catheter attached to a manometer was inserted into the right ventricle by way of the right external jugular vein. The inertia of the system was such that only the pressure during diastole was recorded, i.e., the venous filling pressure. Cardiac output, arterial pressure, and peripheral venous pressure were also measured.

It was found that occlusion of the common carotid arteries, irrespective of whether or not the vagi were intact, caused a rapid, sustained increase in right intraventricular pressure. Release of the carotid occlusion was followed by a slow fall of pressure to the previous level. The acceleration of pulmonary blood flow which accompanied occlusion of the carotid arteries was attributed to the increased pressure in the right ventricle.

LAPLACE.

Vazquez, J. O., Montero, J. C., and Gonzales, P. P.: Transient Right Bundle Branch Block Following Thoracoplasty. Rev. espaň. de cardiol. **1**:246 (May), 1947.

A 33-year-old woman had right bundle branch block for at least seven months following a left-sided thoracoplasty with resection of the first five ribs. Nine months after the operation a normal record was obtained. No other evidence of cardiovascular disease was present. Only one electrocardiogram taken before, one seven, and one nine months after the operation were available.

HECHT.

Tum Suden, Caroline: Effect of Adrenocortical and Sympathicoadrenal Factors on the Cardiovascular Sensitivity to Potassium in the Rat. Am. J. Physiol. 149:589 (June), 1947.

Ergotamine tartrate increased about threefold the susceptibility of intact rats to repeated injections of potassium chloride, as evidenced by circulatory collapse. Moderate deficiencies of adrenocortical activity favor a potassium-induced circulatory collapse by permitting a more rapid rise in extracellular potassium, whereas inactivation of adrenergic mechanisms by sympatholytic agents may sensitize the cardiovascular system of the rat to potassium at low values. The combination of both dysfunctions produced an acute susceptibility to potassium. The increased susceptibility of ergotamine-treated rats to potassium was further enhanced by histamine but histamine itself had no appreciable effect.

BERNSTEIN.

Eckenhoff, J. E., Hafkenschiel, J. H., Landmesser, C. M., and Harmel, M.: Cardiac Oxygen Metabolism and Control of the Coronary Circulation. Am. J. Physiol. 149:634 (June), 1947.

The original purpose of these experiments was to examine the thesis that the coronary vessels, like the cerebral vessels, possess an effective intrinsic control in relation to the metabolic requirements of the tissue. The data do not afford any evidence as to the mechanisms involved in these adjustments, whether nervous or chemical, and, if the latter, the exact identity of the chemical factors. From the demonstration that anoxemia, excess hydrogen ions, acetylcholine, and epinephrine are all capable of dilating the coronary arteries, it is concluded that no one chemical agent need be selected as being solely or predominately involved; the effect is more likely to be due to the consensual and simultaneous effects of all the demands and products of cardiac metabolism. The authors were not able to demonstrate any effective vasomotor control over the coronary circulation under the experimental conditions.

When the blood pressure was increased, cardiac output and cardiac work fell, while cardiac oxygen consumption increased, with consequent decrease in efficiency. When cardiac output was primarily increased, cardiac work, cardiac oxygen consumption, and cardiac efficiency all increased, even though the blood pressure rose concurrently. When, as a result of anoxemia, cardiac output fell while blood pressure and oxygen consumption remained unchanged, cardiac efficiency decreased. All this suggests that a fall in blood pressure without a decrease in cardiac output, such as may occur in spinal anesthesia or circulatory collapse, may not be as ominous as it is generally believed to be.

The heart appears to be safeguarded against anoxia by three mechanisms: (a) decreased tonus in the coronary vessels; (b) diversion of a relatively larger fraction of total cardiac output to the coronary circulation; (c) decreased cardiac work, perhaps associated with increased cardiac efficiency consequent to the fall in aortic pressure.

BERNSTEIN.

Karpovich, Peter V.: Breath Holding as a Test of Physical Endurance. Am. J. Physiol. 149:720 (June), 1947.

Since many previous investigators had considered breath holding as a test of cardiorespiratory fitness, it was decided to find the relationship between breath holding and standard physical activities which place considerable demands upon the cardiorespiratory function. As determined, the coefficients of correlation between the breath holding tests and the treadmill running time and the Harvard test score are not statistically significant. For this reason, breath holding tests cannot be used for prediction of endurance. The time the breath can be held apparently measures the ability to withstand the discomfort caused by breath holding and in no way assesses physical fitness.

BERNSTEIN.

American Heart Association, Inc.

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Program of the Twenty-First Scientific Sessions of the American Heart Association, June 18-19, 1948, North Ballroom, Stevens Hotel, Chicago, Ill.

Essayists, except the George Brown Memorial Lecturer, will be restricted to fifteen minutes; discussors, to three minutes. Each discussor will speak from the rostrum after a notation including his name, address, and the presentation to be discussed has been handed to the secretary. Questions lacking general interest should be directed to essayists privately after discussion has been completed. Each essayist must leave his manuscript with the presiding officer. All manuscripts will be considered the property of the American Heart Association, and will be forwarded to the Editor of the American Heart Journal for consideration for publication in that Journal.

First Session 2:00 P.M., Friday, June 18
Second Session 9:00 A.M., Saturday, June 19
Third Session 2:00 P.M., Saturday, June 19

The following is the program of papers to be read to the Scientific Sessions:

"George Brown Memorial Lecture," by Edgar V. Allen, Mayo Clinic, Rochester, Minn.

"A Clinical Study of Subacute Bacterial Infection Confined to the Right Side of the Heart or the Pulmonary Artery," by Paul S. Barker, University of Michigan Medical School, Ann Arbor, Mich.

"Plasma and Blood Infusion Following Myocardial Infarction," by John J. Sampson and Isidore M. Singer, Harold Brunn Institute for Cardiovascular Research, Mt. Zion Hospital, San Francisco, Calif.

'Report of the Committee for the Evaluation of the Use of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction," by Irving S. Wright, Chairman, New York, N. Y.

"Animadversions Upon the Nature and Cure of the Dropsy; Particularly on the Optimal Intake of Water for Edematous Cardiac Patients," by Ferdinand R. Schemm, Great Falls Clinic, Great Falls, Mont.

'Surgical Treatment of Aneurysms of the Aorta and Its Large Branches," by Gerald H. Pratt, New York Hospital, New York, N. Y.

"The Diagnosis of Interauricular Septal Defect," by Richard S. Cosby and George C. Griffith, Los Angeles County General Hospital, Los Angeles, Calif.

"Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding," by Alfred Steiner, Forrest E. Kendall, and Margaret Bevans, First (Columbia) Division, Goldwater Memorial Hospital, New York, N. Y.

"Arterectomy in the Treatment of Ischemic Neuritis Following Arterial Occlusion," by Norman E. Freeman, Frank H. Leads, and Richard E. Gardiner, University of California Medical School, San Francisco, Calif.

"Differentiation of the Change in the Q-T Interval of the Electrocardiogram in Hypocalcemia and Hypopotassemia," by A. Carlton Ernstene and William L. Proudfit, Cleveland Clinic, Cleveland, Ohio.

"Studies on the Circulation With the Use of Radio-Active Tracers," by Myron Prinzmetal, Cedars of Lebanon Hospital, Los Angeles, Calif.

"The Water Tolerance of the Hypertensive Patient: Its Relation to Operability," by Geza de Takats and Edson F. Fowler, University of Illinois College of Medicine, Chicago, Ill.

"Clinical Studies on Twenty-One Cases of Coarctation of the Aorta," by M. J. Shapiro, Children's Heart Hospital, Minneapolis, Minn.

"Normal and Impaired Function of the Superficial Veins," by J. B. Hickam and R. P. McCulloch, Duke University School of Medicine, Durham, N. C.

"Pathology of the Pulmonary Arterioles in Aortic Coarctation Associated With Patent Ductus Arteriosus," by Jesse E. Edwards, Howard B. Burchell, and Norman A. Christensen, Mayo Clinic, Rochester, Minn.

"Studies of Arterial Oxygen Saturation in Patients With Suspected Arterial Hypoxemia Utilizing a Modified Oximeter," by J. E. Jeraci, G. E. Montgomery, and E. H. Wood, Mayo Clinic, Rochester, Minn.

"Biomicroscopy of Conjunctival Vessels in Hypertension," by Arthur Lack, Travis Winsor, William Adolph, and Walter Ralston, University of Southern California School of Medicine, Los Angeles, Calif.

"Correlation Between the Decrease in Coronary Flow and the Electrocardiographic Changes in Progressive Coronary Occlusion," by Rene Wegria, Marcel Seegers, and Richard P. Keating, Presbyterian Hospital, New York, N. Y.

Papers to be read of time permits.

"Cardiac Effects of Non-Pressor Sympathomimetic Compounds," by M. H. Nathanson, University of Southern California School of Medicine, Los Angeles, Calif.

"Dissecting Aneurysm of the Aorta in World War II: Clinical and Pathological Study of Eighty-Five Cases," by Vincent J. Seiwert and Ira Gore, Army Institute of Pathology, Washington, D. C.

"The Pathogenesis of Diastolic Hypertension," by Peter Heinbecker, Washington University School of Medicine, St. Louis, Mo.

"The Heart in the Terminal State: Effect of Intracardiac Epinephrine," by Edward Massie, Charles H. Huguley, and Hyman S. Stillerman, Washington University School of Medicine, St. Louis, Mo.

"The Use of Veratrum Viride in the Treatment of Essential Hypertension," by Edward D. Freis, Joseph R. Stanton, and Robert W. Wilkins, Boston University School of Medicine, Boston, Mass.

"Evaluation of Three Methods for Determining the Rate of Dissipation of Digoxin in Man," by Robert C. Batterman and Arthur C. DeGraff, New York University College of Medicine, New York, N. Y.

"The Clinical Significance of the U Wave in the Electrocardiogram," by Stephen Elek, L. S. Gottlieb, and George C. Griffith, University of Southern California School of Medicine, Los Angeles, Calif.